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The LC50 was less than 0.5 mg/l for mice (i.e., 50% of the mice in the 96.6 mg/m3 of air dose group died), the trigger for reporting.

Abstract

The acute respiratory tract sensory irritation potency of Desmodur VP LS 2294 was evaluated in young adult male Wistar rats and male OF1 mice. Groups of four animals per group and species were simultaneously exposed to actual concentrations of the aerosolized Desmodur VP LS 2294 without any additional vehicle. The duration of exposure to the Desmodur VP LS 2294 was approximately 3 hours. All animals were sacrificed after a 1-week post-exposure period.

With regard to the intensity of changes of breathing patterns as well as clinical findings, mice appeared to more sensitive than rats. Therefore, toxicological assessment was focused on the results obtained with mice. 3.9 mg/m3 of air was tolerated without any clinical signs, changes in body weight or appreciable effect on breathing pattern. Mice exposed to the next higher concentration (15.5 mg/m3 of air) elicited an unregular breathing pattern and a concentration-dependent decrease in tidal volume without appreciable changes in respiratory rate. An increase in respiratory rate was seen at concentrations equal to or exceeding 37.8 mg/m3 of air. Mortality (50%) occurred in mice exposed to 96.6 mg/m3 of air. An apparent relationship of lung edema formation and mortality was observed.

It was observed that Desmodur VP LS 2294 caused an apneic pause between the end of expiration and inspiration and a concentration-dependent decrease in tidal volume, however, without appreciable concentration-dependent changes in respiratory rate. At exposure concentrations equal to or exceeding 37.8 mg/m3 of air, an increase in the respiratory rate was observed. Conclusive exposure-duration related exacerbation of effects could not be ascertained during the 3-hour exposure period. The shallower breathing pattern, as a response to Desmodur VP LS 2294, is thought to have been caused by a vagally mediated reflex originating from the stimulation of the pulmonary C fibers. The change in respiratory patterns thus indicate that this effect is dominated by the stimulation of receptors located in the lower- rather than the upper-respiratory tract. Due to this mode of action, no emphasis was made to calculate an RD50-value.

BAYER AG
DEPARTMENT OF TOXICOLOGY
FRIEDRICH-EBERT-STR. 217-333
D - 42096 WUPPERTAL

Report-No.: PH 28522

Date: 26.02.1999

DESMODUR VP LS 2294

**RD₅₀-DETERMINATION ON RATS AND MICE
According to the ASTM E981-84 method**

by

PD Dr. J. Pauluhn

Study No.: T3067460


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GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with the OECD Principles of Good Laboratory Practice (as revised in 1997) and to the Principles of Good Laboratory Practice (GLP) according to Appendix 1 German Chemicals Act (Bundesgesetzblatt Part I, July 29, 1994).

Notice: On October 2, 1998 (see pp. 46) one group of animals was exposed in a 'pre-test' (sighting study). As already all objectives of study were fulfilled, this 'pre-test' group is incorporated in this report as if it had been a 'main-study' group.



PD Dr. J. Pauluhn D.A.B.T.
Board Approved Toxicologist (DGPT)
EUROTOX Registered Toxicologist
Study Director

Date: FEB. 12, 1999

SPONSOR:
BAYER CORP.

Dr. J. Thyssen
Head of Toxicology

Date: _____

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Quality Assurance Statement**Test Item :** DESMODUR VP LS 2294**Study No.:** T3067460

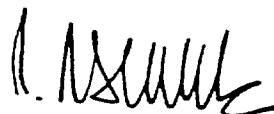
Study-based inspections/audits were conducted by the Quality Assurance on the dates given below. Audit reports have been submitted in writing to the study director and, if necessary, also to the laboratory management, or other persons affected.

Date of audit**Date of report to study
director and/or management**

09/ 25/ 1998	(study plan)	09/ 25/ 1998
10/ 08/ 1998	(study conduct)	10/ 08/ 1998
10/ 15/ 1998	(study conduct)	10/ 16/ 1998
01/ 13/ 1999 - 01/ 29/ 1999	(first draft)	02/ 05/ 1999
02/ 16/ 1999	(final draft)	02/ 23/ 1999

The results of the study and the methods used have been correctly reported.

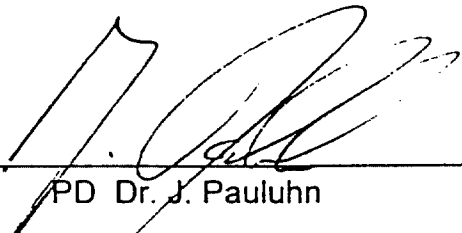
Quality Assurance Unit
PH-QA-C/GLP, Bayer AG

Date:Feb. 23, 1999**Responsible:**

Dr. R. Rauchschalbe

3. SIGNATURES


Study
Director:



PD Dr. J. Pauluhn

Date: Feb. 12, 1999


Analytical characterization
of test atmospheres:



Dr. W. Rüngeler

Date: Feb. 12, 1999

Department
Head:



Dr. E. Bomhard

Date: Feb. 26, 1999

4. SUMMARY

The acute respiratory tract sensory irritation potency of DESMODUR VP LS 2294, hereafter referred to as *test substance*, has been conducted in young adult male Wistar rats and male OF1 mice. Groups of animals (four animals per group and species) were simultaneously exposed to actual concentrations of the aerosolized test substance of 0 (conditioned air), 3.9, 15.5, 37.8, and 96.6 mg/m³ air¹. The test substance was aerosolized without any additional vehicle. The duration of exposure to the test substance was approximately 3-h. All animals were sacrificed after a 1-week postexposure period. The procedures applied were largely consistent with the ASTM E981-84 method. The aerosol generated was of adequate respirability (i.e. MMAD \approx 1.2 μ m, GSD \approx 1.5) and hence meets the criteria of internationally recognized recommendations (SOT, 1992).

Results: With regard to the intensity of changes of breathing patterns as well as clinical findings, mice appeared to be more sensitive than rats. Therefore, toxicological assessment is focusing on the results obtained with mice. 3.9 mg/m³ air was tolerated without any clinical sings, changes on body weights or appreciable effects on breathing pattern. Mice exposed to the next higher concentration (15.5 mg/m³) elicited an irregular breathing pattern and a concentration-dependent decrease in tidal volume. An increase in respiratory rate was seen at concentrations of 15.5 and 37.8 mg/m³ whereas the increase in respiratory rate during exposure to 96.6 mg/m³ was transient. Mortality (50%) occurred in mice exposed to 96.6 mg/m³. An apparent relationship of lung edema formation and mortality was observed.

In the present study, it is observed that the respirable aerosol of DESMODUR VP LS 2294 caused an apneic pause between end of expiration and inspiration and a concentration-dependent decrease in tidal volume, however, without conclusive, i.e., concentration-dependent changes in respiratory rate. Marked exposure-duration related exacerbation of effects could not be ascertained during the 3-h exposure period. The change in respiratory patterns thus indicate that this effect is dominated by the stimulation of receptors located in the lower- rather than upper-respiratory tract.

Due to this mode of action (lower respiratory tract irritation), a calculation of a RD₅₀-concentration was not attempted. The non-irritant threshold concentration is considered to be 3.9 mg/m³ air.

¹ Concentrations represent actual breathing zone concentrations based on analyses utilising the derivatization of the test agent (nitro-reagent / HPLC).

5. INTRODUCTION

This study served the purpose to assess irritant-induced immediate-onset changes in respiratory function during a single 3-h inhalation exposure according to previously published methods (Pauluhn and Eben, 1991) using a respirable DESMODUR VP LS 2294 aerosol as test substance. The study was performed on male rats and male mice (nose-only exposure over 3-h to the aerosol atmospheres of the test substance, dynamic exposure conditions, 1-week postexposure observation period). The procedures applied were largely consistent with the ASTM E981-84 method which stipulates the use of mice rather than rats. Rats, however, were additionally used for the purpose to compare the results of this study with an acute inhalation study on rats. Exposure of mice and rats was simultaneous.

Testing facility:

Institute of Toxicology - Industrial Chemicals/Department of Occupational Toxicology,
Bayer AG, D-42096 Wuppertal, Friedrich-Ebert-Straße 217 - 333, Germany.

Study/project identification:

Study no.: T3067460

Study period:

October 2, 1998 - October 16, 1998

Experimental starting date: September 22, 1998 (technical pre-trials)

Study completion date: see signature of study director (page 7)

Sponsor:

BAYER Corporation, Agriculture Division
P.O. Box 4913 Hawthorn Road
Kansas City, MO 64120-0013
U.S.A.

6. RESPONSIBILITIES

Air conditioning/air make-upDipl. Ing. G. Strietholt
Analytical characterization of test atmospheres:..... Dr. W. Rüngeler
Analytical characterization of test substance prior to testing: D.I. Jahn/Bayer AG
Archiving the study data:..... Prof. G. Schlüter
Biometric evaluation:..... Dr. J. Pauluhn
Gross pathology:.....Dr. Rosenbruch
Head of Department:..... Dr. E. Bomhard
Laboratory Animal Services: Dr. Petersen v. Gehr
Quality Assurance:..... Dr. H. Lehn
Study Director and Report Author:..... Dr. J. Pauluhn
Test substance shipment / supply of data:..... Dr. Dislich/Bayer AG

7. MATERIALS AND METHODS

7.1. Test substance

Test substance: Desmodur VP LS 2294 (= Desmodur TP LS 2294) a polymerisate on the basis of hexamethylene diisocyanate, i.e., a Desmodur® N 3300 - like pre-polymer

CAS#: 28182-81-2

Manufacturer: BAYER AG, Leverkusen

Lot-no.: 8003 , approval date: June 25, 1998

Purity: within specification.
monomeric HDI: < 0.3%
symmetrical HDI-isocyanurate and higher oligomers 50 - 60%
asymmetrical HDI-iminooxadiazindion and higher oligomers 40 - 50%; both products have the same CAS-no (Hexane, 1,6-diisocyanato-, homopolymer)

Storage conditions: at room temperature / darkness (handling under N₂-atmospheres to exclude contact with humidity). Stability was guaranteed during the course of study.

Appearance: clear to yellowish liquid

7.2. Test system and housing of animals

Species and species justification: The study was carried out on male rats and male mice, rodent species commonly used in inhalation toxicity studies.

Healthy young adult SPF bred Wistar rats, strain Cpb:WU (SPF), from the experimental animal breeder Harlan-Winkelmann GmbH, Borcheln, Germany, and healthy young adult SPF bred mice, strain ICO:OF1 (I.O.P.S. Caw), from the experimental animal breeder IFFA Credo, Belgium, were used. Animals of these strains have been used at Bayer AG in this type of studies for years. Historical data on their physiology, diseases and spontaneous alterations are available. The state of health of the strain is randomly checked at the instance of the Laboratory Animal

Services, Bayer AG, for the most important specific infectious pathogens. The results of these examinations are archived.

Acclimatization: The animals were acclimatized to the animal room conditions for at least 5 days before use.

Identification: Animals were identified by both individual color-marking and cage-labels. All animals from this study were located on one cage-rack.

Randomization: Before the start of the study the health status of each animal was assessed. Animals were subsequently assigned to exposure groups at random (randomization procedure is described in the respective section 'Statistical Evaluation of Data').

Health status: Only healthy animals free of signs were used for this study. The animals were not vaccinated or treated with anti-infective agents either before their arrival or during the acclimatization or study periods.

Age and weight: At the study start the variation of individual weights did not exceed ± 10 per cent of the mean (see Appendix). Rats and mice were approximately 2 and 1 months old, respectively, at the commencement of test.

Animal housing: During the acclimatization and study periods the animals were housed in conventional Makrolon® Type II (mice) and III (rats) cages, four per cage (based on A. Spiegel and R. Gönnert, Zschr. Versuchstierkunde, 1, 38 (1961) and G. Meister, Zschr. Versuchstierkunde, 7, 144-153 (1965)). Cages were changed twice a week while unconsumed feed and water bottles were changed once per week. The legal requirements for housing experimental animals (86/609 EEC) were followed.

Bedding: Bedding consisted of type S 8/15 low-dust wood granulate from Ssniff, Soest/Westfalen, Germany. The wood granulate was randomly checked for harmful constituents at the request of the Laboratory Animal Services, Bayer AG.

Animal rooms: All animals of this study were housed in a single room. Mistakes in animal assignments were excluded by adequate spatial separation (separate cage racks), clear cage labeling, and appropriate organization of all work procedures.

Environmental conditions in the animal room

The animal room environment was as follows:

Room temperature:	22 ± 2 °C
Relative humidity:	approximately 50 %
Dark/light cycle:	12 h/12 h; artificial light from 6.00 a.m. to 6.00 p.m. Central European Time
Light intensity:	approximately 14 watt/m ² floor area
Ventilation:	approximately 10 air changes per hour

The room humidity and temperature were continuously monitored and documented using a calibrated thermohygrograph. Occasional deviations from these conditions occurred, e.g. as a result of animal room cleaning, but these had no detectable influence on the outcome of this study.

Cleaning, disinfection, and pest control: The animal room was regularly cleaned and disinfected once a week with an aqueous solution of Tego® 2000. Contamination of the feed and contact with the test system were excluded. Pest control was not conducted in the animal room.

Feeding: Ration consisted of a standard fixed-formula diet (Altromin® 1324 pellets maintenance diet for rats and mice, Altromin GmbH, Lage) and tap water (drinking bottles). Both food and water were available *ad libitum*. The pelletized feed was contained in a rack in the stainless-steel wire cage cover. The nutritive composition and contaminant content of the standard diet was checked regularly by random sampling by the Laboratory Animal Services, Bayer AG. Details concerning general feed and water specifications are provided in the Appendix.

Water: Drinking quality tap-water (Drinking Water Decree of 05.12.1990, Bundesgesetzblatt [federal law gazette] part I, page 2612) was provided *ad libitum* in polycarbonate bottles containing approximately 300 ml (based on A. Spiegel and R. Gönnert, Zschr. Versuchstierkunde, 1, 38 (1961) and G. Meister, Zschr. Versuchstierkunde, 7, 144-153 (1965)). The results of feed and water analyses are retained by Bayer AG. The available data provided no evidence of an impact on the study objective.

7.3. Test Guidelines

The study described below was carried out in accordance with OECD Guideline No. 403. The study conditions were adjusted so as to fulfill both the EC Guideline 92/69/EEC, FIFRA § 81-3 (US EPA, 1984) OPPTS 870.1300 (US EPA, 1998) guidelines. Other recommendations (US EPA, 1988; ASTM E981-84; SOT, 1992) were also considered so as to comply with internationally recognized procedures for this type of bioassay.

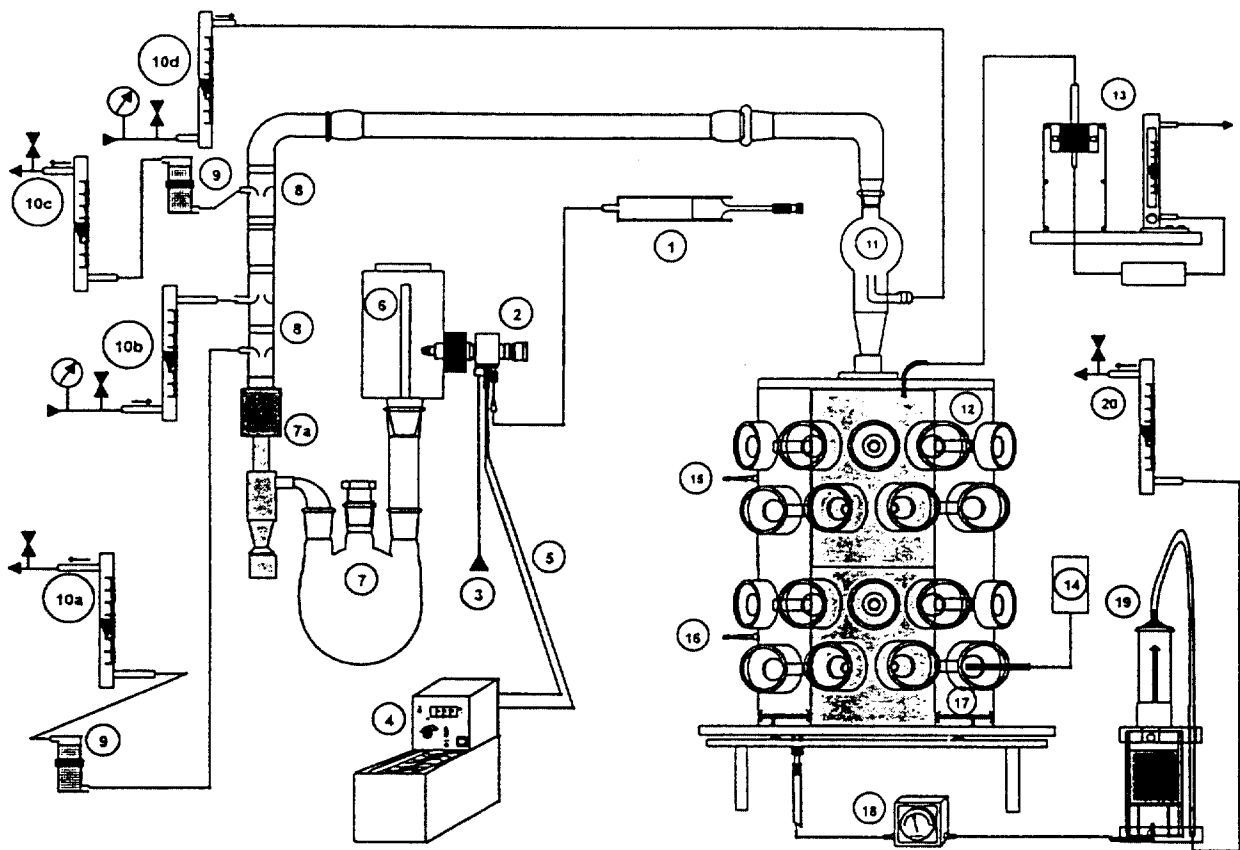
7.4. Exposure Conditions

Mode of exposure: Animals were exposed to the aerosolized test substance in Plexiglas exposure tubes applying a *directed-flow* nose-only exposure principle (Moss and Asgharian, 1994). The exposure tube was modified as flow-plethysmograph ($p = \text{const.}$). This type of exposure is preferable to whole-body exposure on scientific (Pauluhn, 1984) and technical reasons (rapid attainment of steady-state concentrations, no problems with regard to test atmosphere inhomogeneities, better capabilities to control all inhalation chamber parameters, easier cleaning of exhaust air, lower consumption of test substance, and concomitant examination of respiratory patterns). The chambers used are commercially available (TSE, 61348 Bad Homburg) and the performance of this type of chamber has been published (Pauluhn, 1984; Pauluhn, 1988; Pauluhn, 1994).

Vehicle: The test substance was aerosolized neat without any vehicle.

7.5. Aerosol Generation and Exposure Technique

Generation of atmosphere: A modified Schlick-nozzle Type 970, form-S 3 (Schlick GmbH, Coburg, Germany) was used to disperse the test substance into air. For nebulization, conditioned (dry, oil free) compressed air (15 L/min, dispersion pressure approximately 600 kPa) was used. The nozzle was kept at approximately room temperature (group 2, see Table 1) or 50 °C (group 3-5, see Table 1) using a water jacket connected to a digitally controlled thermostat. The increase of temperature within the nozzle resulted in a marked decrease in viscosity and hence increased the aerosol output. The respective target concentrations were achieved by extraction/dilution cascades. Further details are summarised in Figure 1 and Table 1 (see result section).

Figure 1: Inhalation Chamber (schematic)

1. Metering pump with test substance	11. Cyclone / air mixing
2. Binary nozzle with water jacket	12. Directed-flow nose-only chamber
3. Pressurized, conditioned air	13. Photometer (real-time aerosol monitoring)
4. Thermostat for water jacket	14. Digital thermometer
5. Tubing to nozzle	15. Filter sampling / sampling for particle-size analyses
6. Pre-separator / baffle	16. Sampling for nitro-reagent analyses
7. Glass flask	17. Chamber exhaust air
7a. Cyclone	18. Humidity measurement
8. Dilution cascade	19. Cotton-wool aerosol filter + HEPA filter
9. Cotton-wool filter	20. Digitally controlled vacuum
10a-d. Conditioned air for dilution of atmospheres	

Description of apparatus: Dry conditioned air was used to aerosolize the test substance so as described above. After nebulization, the test substance was conveyed into the inner plenum of the inhalation chamber, the test atmosphere was then forced through openings in the inner concentric cylinder of the chamber, directly

towards the animals' breathing zone. This *directed-flow* arrangement minimizes re-breathing of exhaled test atmosphere. The stability of the test atmosphere was monitored continuously using an aerosol photometer as real-time monitoring device (*vide infra*). Two inhalation chamber segments were used each one suitable to accommodate 20 small laboratory animals at the perimeter location. A slight positive balance between the air volume supplied and extracted ensured that no passive influx of air into the exposure chamber can occur. The slight positive balance provides also adequate dead-space ventilation of the exposure restrainers (plethysmographs). The pressure difference between the inner inhalation chamber and the exposure zone was 0.02 cm H₂O (Pauluhn, 1994). The exposure system was accommodated in an adequately ventilated enclosure. Temperature and humidity were measured by using robust sensors and were placed in the inhalation chamber as shown in Fig. 1. Further technical details are provided in the ensuing sections.

Inhalation Chamber: Each segment of this aluminum inhalation chamber has the following dimensions: inner diameter = 14 cm, outer diameter = 35 cm (two-chamber system), height = 25 cm (internal volume = about 3.8 l). The construction of the inhalation chamber is shown schematically in Fig.1. Details of this modular chamber and its validation have been published previously (Pauluhn, 1994).

Inhalation chamber steady-state concentration: The test atmosphere generation conditions provide an adequate number of air exchanges per hour (> 200 x, continuous generation of test atmosphere). Under such test conditions steady-state is attained within approximately one minute of exposure ($t_{99\%} = 4.6 \times \text{chamber volume} / \text{flow rate}$; McFarland, 1976). The ratio between the air supplied and exhausted was chosen so that approximately 90% of the supplied air is removed from the chamber as exhaust. The remainder provides adequate dead-space ventilation for the exposure tubes. At each exposure port a minimal air flow rate of 0.75 L/min was provided. The test atmosphere can by no means be diluted by bias-air-flows. The inhalation chamber was operated in a well ventilated chemical fume hood.

Optimization of respirability: In order to increase the efficiency of the generation of respirable particles and to prevent larger particles from entering the chamber a PVC-pre-separator/baffle system was used (Tillery et al., 1976; Pauluhn, 1994). Additionally (see Fig. 1 for details), an URG, Carrboro, NC, cyclone was used (ECD 2.5 μm @ flow-rate 10 L/min).

Conditioning the compressed air: Compressed air was supplied by Boge compressors and was conditioned (i.e. freed from water, dust, and oil) automatically by a VIA compressed air dryer. Adequate control devices were employed to control supply pressure.

Air flows: During the exposure period air flows were monitored continuously and, if necessary, readjusted to the conditions required. Air flows were measured with calibrated flow-meters and/or soap bubble meter (Gilibrator, Ströhlein Instruments, Kaarst) and were checked for correct performance at regular intervals.

Treatment of exhaust air: The exhaust air was purified via cotton-wool/HEPA filters. These filters were disposed of by Bayer AG.

7.6. Inhalation chamber temperature and humidity

The temperature and humidity measurements were made using a digital thermometer (breathing zone area) and Lambrecht hygrometer (measurement in exhaust air). The values were recorded at intervals of 30 min. The humidity sensor was previously calibrated using saturated salt solutions according to Greenspan (1977). The temperature sensor was previously calibrated with a calibration thermometer. Details of this monitoring system have been reported elsewhere (Pauluhn, 1986).

7.7. Analysis of the test atmosphere

Nominal concentration: The nominal concentration was calculated from the ratio of the quantity of test substance sprayed into the baffle and the total throughput of air through the inhalation chamber. The lower analytical concentrations compared with the nominal concentrations are attributed to the efficient removal of larger particles in the baffle/preseparator system.

Gravimetric concentration: The test-substance concentration was determined by gravimetric analysis (filter: Glass Fiber-Filter, Sartorius, Göttingen, Germany). Gravimetric analyses were performed once during exposure to allow for direct comparisons with gravimetric cascade impactor analyses.

Analytical concentration: The exposure atmospheres were characterized using the nitro-reagent derivatization technique (nitro-reagent: N-4-nitrobenzyl-N-n-propyl-ammonium chloride). Further methodological details related to sampling as well as characterization of test atmosphere are provided in the Appendix. For reference/calibration purposes the test compound was used.

Chamber samples were taken in the vicinity of the breathing zone (see Fig. 1). The number of samples taken was sufficient to characterize the test atmosphere and was

adjusted so as to accommodate the sampling duration and/or the need to confirm specific concentration values. Optimally, samples were collected after the inhalation chamber equilibrium concentration had been attained (sampling frequency see Appendix). All analytical concentrations reported refer to mg DESMODUR VP LS 2294/m³ air.

7.8. Characterization of Aerodynamic Particle-Size Distribution

The samples for the analysis of the particle-size distribution were also taken in the vicinity of the breathing zone. During each exposure period at least one sample was taken.

The particle-size distribution was analyzed using a BERNER-TYPE AERAS critical orifice, low-pressure critical orifice cascade impactor (Hauke, Gmunden, Austria). Specifications and evaluations are provided in the Appendix. The individual impactor stages had been covered by an aluminum foil which was subjected to gravimetric analysis. Due to the physical properties of the test compound, an adhesive stage coating (silicone spray) was not used to prevent particle bounce and re-entrainment. Gravimetric analyses were made using a digital balance.

Evaluation of particle-size distributions

The parameters characterising the particle-size distribution were calculated according to the following procedure:

Mass Median Aerodynamic Diameter (MMAD): Construct a 'Cumulative Percent Found - Less Than Stated Particle Size' table, calculate the total mass of test substance collected in the cascade impactor. Start with the test substance collected on the stage that captures the smallest particle-size fraction, and divide this mass of the test substance by the total mass found above. Multiply this quotient by 100 to convert to percent. Enter this percent opposite the effective cut-off diameter of the stage above it in the impactor stack. Repeat this step for each of the remaining stages in ascending order. For each stage, add the percentage of mass found to the percentage of mass of the stages below it. Plot the percentage of mass less than the stated size versus particle size in a probability scale against a log particle-size scale, and draw a straight line best fitting the plotted points. A weighted least square regression analysis may be used to achieve the best fit. Note the particle size at which the line crosses the 50% mark. This is the estimated Mass Median Aerodynamic Diameter (MMAD).

Calculation of **Geometric Standard Deviation (GSD)**: Refer to the log probability graph used to calculate the Mass median aerodynamic diameter. Provided that the line is a good fit to the data, the size distribution is log normal, and the calculation of the Geometric Standard Deviation is appropriate. Note that particle size at which the line crosses the 84.1% mark. Note the particle size at which the line crosses the 50% mark and calculate as follows: $GSD = 84.1\% \text{ mark} / 50\% \text{ mark}$.

To verify graphically that the aerosol is in fact unimodal and log-normally distributed the normalized mass per stage (f_H') is evaluated as a histogram. $\Delta \log D_p$ is equal the difference $\log D_{p+1} - \log D_p$, whereas D_p is the lower cut-size limit and D_{p+1} the higher cut-size limit of the corresponding impactor stage. Calculate the histogram f_H' by equation:

$$f_H' = \frac{1}{N_f} \times \frac{\text{mass / stage}}{\Delta \log D_p} \quad (1)$$

Calculate the log-normal mass distribution $y'(D_{ae}) = 1/N_f \times y(D_{ae})$ as a function of the aerodynamic diameter (D_{ae}) using by equation:

$$y'(D_{ae}) = \exp \left[-\frac{(\log D_{ae} - \log MMAD)^2}{2 \times \log^2 GSD} \right] \quad (2)$$

and use the normalization factor (N_f):

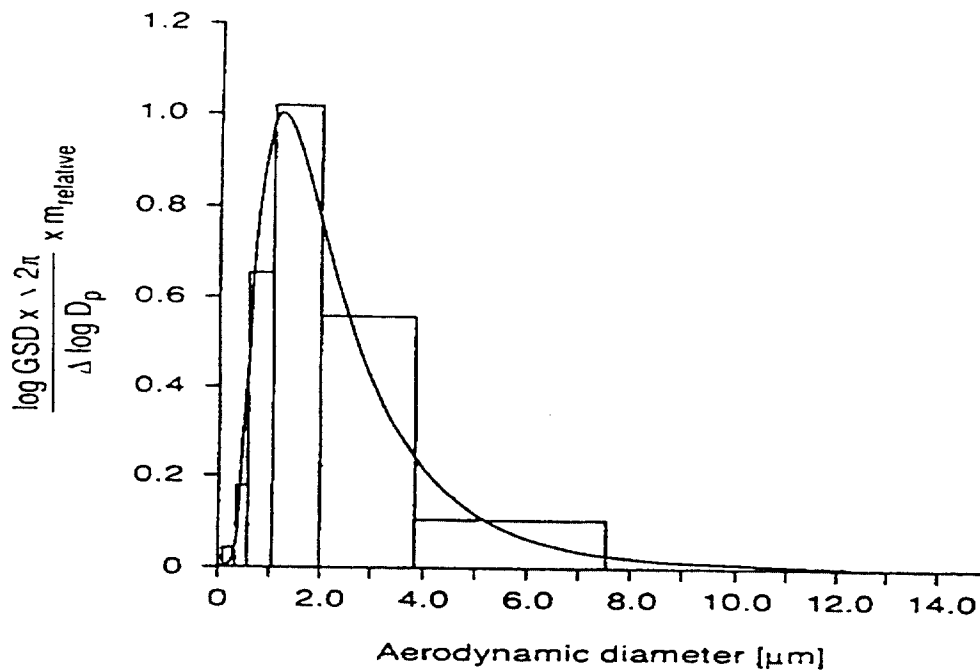
$$N_f = \left(\frac{\Sigma \text{mass}}{\log GSD \times \sqrt{2\pi}} \right)^{-1} \quad (3)$$

It should be noted that for the graphical display of data the size distributions shown in Fig. 2 is constructed utilising equation 2.

The relative mass with an aerodynamic diameter $\leq 3 \mu\text{m}$ ("respirable mass fraction") [Raabe, 1982; Snipes, 1989; SOT-Commentary, 1992] is calculated from the regression line. For probit transformation and linear regression FORTRAN algorithms published by Rosiello *et al.* (1977) are used. The MMAD was calculated using

published following formulas (Marple and Rubow, 1980; Pauluhn, 1994; USP XXII, 1992).

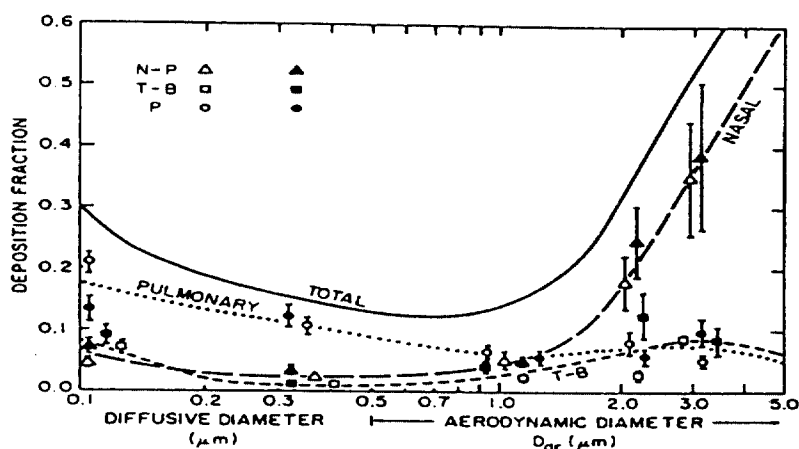
Figure 2: Principle of characterization of aerosol atmosphere



The algorithm for the calculation of particle size characteristics is taken from pertinent reference works on aerosol physics (Dennis, 1976; Marple and Rubow, 1980) and proves to be generally applicable (Pauluhn 1988; Pauluhn, 1994).

Respirability

Fig. 3 below, demonstrates that the particle-size distribution achieved is adequate to reach all potential target structures of the respiratory tract of small laboratory rodents.

Fig. 3 Respirability of Aerosols - Rats (Raabe, 1982)

7.9. Collection Efficiency

The sampling equipment was adjusted with calibrated flow meters to internationally recognized standards (ACGIH, 1978; Section I "Calibration of Air Sampling Instruments").

The conditions for generating the test atmosphere are optimized to provide maximum aerosol respirability to rats and other small laboratory rodents (Raabe, 1982; Snipes, 1989; SOT-Commentary, 1992). The absence of larger particles and high flow rates in the vicinity of the sampling ports make it possible to disregard potential anisokinetic sampling errors, thus ensuring a representative sampling even with different sampling probe orifice diameters and flow rates. The tolerance limits for the radius of the probe orifice are calculated using the following formula [ACGIH, 1978]. Calculations consider both a particle size distribution that encompasses aerodynamic diameters (D_{ae}) of 0.5 to 7.4 μm and sample flows ranging from 8 to 80 ml/sec.

$$5 \times 3 \sqrt{\frac{\text{flow} \times \tau}{4 \times \pi}} \leq r_p \leq \frac{1}{5} \times 2 \sqrt{\frac{\text{flow}}{g \times \tau \times \pi}}$$

r_p = radius of the sample probe in cm = $\frac{1}{2} \times D_p$
 τ = relaxation time (D_{ae} 0.5 μm = 1×10^{-6} sec; D_{ae} 7.4 μm = 1.7×10^{-4} sec)
 g = gravity constant = 980 cm/sec²

Tolerance limits calculations for the sample probe orifice (r_p) indicated that a representative sampling is assured when the orifice inner diameter is in the range of

1.0 to 1.6 cm. Orifices of the sampling instruments used here are in compliance with this criteria. Details of the D_p tolerance limit calculations are published elsewhere (Pauluhn, 1988; Pauluhn, 1994).

7.10. Stability of the Test Atmosphere

The integrity and stability of the aerosol generation and exposure system was measured by using either a RAM-1 or RAS-2 real-time aerosol photometer (MIE, Bedford, Massachusetts, USA). Samples were taken continuously from the vicinity of the breathing zone.

This chamber monitoring allows for an overall survey of toxicologically relevant technical parameters (inlet and exhaust flows as well as atmosphere homogeneity, temporal stability, and generation performance). Interruptions in exposure (e.g. resulting from obstruction of the nozzle or other technical mishaps) are recorded and, if applicable, a commensurate interval is added to the exposure duration for compensation.

7.11. Number of animals

Four male rats and four male mice per group were simultaneously exposed to each concentration under *directed-flow* nose-only conditions for approximately 3-h plus 15-min pre-exposure and 15-min post-exposure periods.

7.12. Control Animals

To identify exposure-related effects, comparisons with the respective air control is conducted. The control animals were exposed similar exposure conditions as were used for the test substance.

7.13. Body weights and duration of observation period

Body weights were measured before exposure and on days 1, 3 and 7. All animals were sacrificed after a 1-week postexposure period.

7.14. Clinical signs

The appearance and behavior of each animal was examined carefully several times on the day of exposure and at least once per day thereafter. Assessments from restraining tubes were made only if unequivocal signs occurred (e.g. spasms, abnormal movements, severe respiratory signs). Following exposure, observations are made and recorded systematically; individual records are maintained for each animal. Cage-side observations included, but were not limited to, changes in the skin and fur, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous system, and somatomotor activity and behavior pattern. Particular attention was directed to observation of tremors, convulsions, salivation, diarrhea, lethargy, somnolence and prostration. Since these signs can only be assessed adequately from freely moving animals, no specific assessment was performed during exposure while animals were restrained.

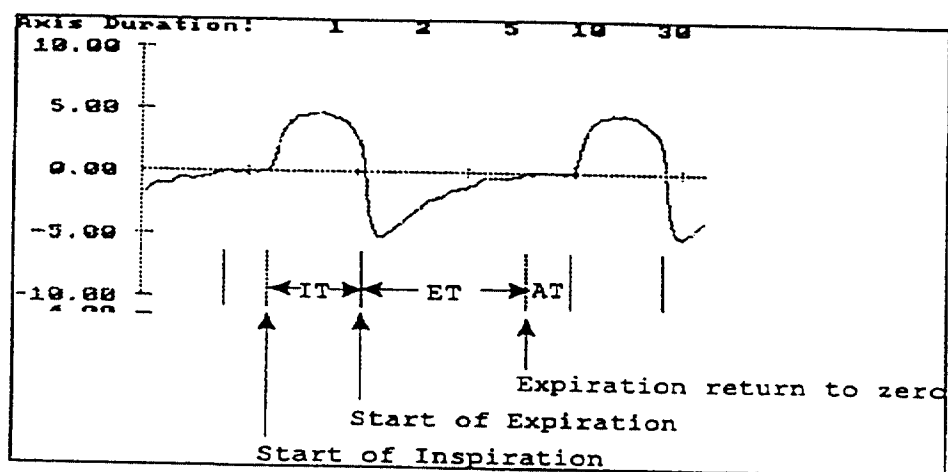
7.15. Respiratory Function Measurements

Measurements were conducted with spontaneously breathing, conscious animals in modified nose-only exposure tubes used as plethysmographs ($p=const.$). The animals were acclimatized to the exposure conditions for an adequate period of time (approx. 15 min). Animals were considered acclimatized when the respiratory rate was in compliance with previous data. The PO-NE-MAH / PLUGSYS Data Acquisition, Analysis & Archive System (supplied and maintained by H. Sachs, March, Germany) was used for measurements. To prevent undue stress of mice when positioned into the plethysmographs a superficial, brief inhalation narcosis (Halothane, 4% v/v in air) was used.

After acclimatization baseline parameters were measured for approximately 15-min (exposure to air). The duration of exposure to the test substance was 3-h, followed by postexposure measurements of 15-min. Measurements were made with four rats and four mice simultaneously. For evaluation of reactions occurring during challenge exposures the following respiratory parameters were evaluated: respiratory rate (RR)

[breaths/min], tidal volume (TV) [ml], respiratory minute volume (MV) [ml/min], peak inspiratory and expiratory flow rates (PIF and PEF) [ml/sec], inspiratory (IT) and expiratory times (ET) [msec], the average duration of apnoic period (AT) [msec], and the number of apnoic periods per logging period exceeding 20% of the ET period [# /time interval]. Additional parameters were derived so as shown in the Appendix. Measurements were made in nose-only animal restrainers with wire-mesh style pneumotachograph and differential pressure transducers ($MP 45 \pm 2 \text{ cm H}_2\text{O}$, Validyne) fitted shortly onto the plethysmograph. The head and body compartments were separated using a double-layer latex neck seal. Precautions were taken to avoid artifacts due to restraint and tight fitting seals around the neck. Volumes were calculated by integration of the flow signal from the body compartment and potential artifacts related to the dependence of the calculated volume as a function of respiratory frequency were considered. The resistance to air flow of the wire-mesh screens was adjusted so that artificial volume changes between pump rates of 50-250 cycles/min did not exceed 10%. The validation of the system was performed prior to each exposure individually for all plethysmographs using a calibration volume of 0.3 ml (mice) or 2.0 ml (rats) at a frequency of 200 (mice) or 100 (rats) cycles/min. All signals were averaged for 45 seconds. The flow and volume signals for each individual animal were displayed on the monitor of the IBM-AT computer during measurement. Phase and amplitude checks were documented by re-processing of raw data. Breaths were identified by the software when the PIF exceeded 1 ml/sec. The principle of the evaluation of breathing patterns is illustrated in the following Figure 4.

Figure 4: Flow/volume measurements



7.16. Necropsy

All animals were sacrificed at the end of the observation period using sodium pentobarbital (Nembutal®) (intraperitoneal injection) and were given a gross-pathological examination. Consideration was given to performing a gross necropsy on animals as indicated by the nature of toxic effects, with particular reference to changes related to the respiratory tract. All gross pathological changes were recorded and evaluated.

7.17. Statistical evaluation of data

Body weights: Means and single standard deviations of body weights are calculated. Mean body weights are also depicted graphically as a function of time. Since in acute studies individual group means may differ prior to commencement of the first exposure, the body weight gain was statistically evaluated for each group. For these evaluations a one-way ANOVA (vide infra) is used.

Pulmonary function tests: Mean data (means and standard deviation of the pre-exposure period and the maximum relative changes during exposure) of four animals from each group and for each parameter are reproduced in tabular form in the Appendix. All parameters collected are also reproduced graphically and these data were smoothed using a polynomial function before graphing (low pass filter for outliers). Brief peaks caused by abnormal movements in the plethysmograph were thereby minimized. Different algorithms were used for smoothing of the raw data in the result section and in the Appendix.

Randomization: A computerized list of random numbers served the purpose to assign animals at random to the treatment groups.

Analysis of variance (ANOVA): This parametric method checks for normal distribution of data by comparing the median and mean. The groups are compared at a confidence level of $(1-\alpha) = 95\%$ ($p = 0.05$). The test for the between-group homogeneity of the variance employed Box's test if more than 2 study groups were compared with each other. If the above F-test shows that the intra-group variability is greater than the inter-group variability, this is shown in the Appendix as "*no statistical difference between the groups*". If a difference is found then a pairwise post-hoc comparison is conducted (1- and 2-sided) using the Games and Howell modification of the Tukey-Kramer significance test. This program was originally obtained from BCTIC.

RD₅₀-Calculation: The analysis of regression curves and calculation of their 95%

confidence intervals were performed with the aid of Sigma Plot for Windows (Jandel Scientific, Erkrath, Germany), if applicable. In principle, this calculation is based on the maximum decrease of respiratory rate (group means) which is determined mathematically and graphically. For calculation of the RD_{50} -value the graphically determined decrease in respiratory rate is generally given preference.

Programming and validating software: Software code for the following purposes was written in Microsoft Fortran 77: ANOVA and particle analysis. The computer programs were carefully validated. The validation was conducted using text book data sets (e.g. BCTIC, Gad and Weil, 1982). It should be emphasized, however, that this type of source code validation does not fulfill that type of formal validation required by current GLP-principles. Wherever possible, raw data and calculated values are displayed graphically to provide a versatile opportunity for data comparison.

7.18. Presentation of raw data

Raw data entered into, processed and/or stored by a computer system can be saved and printed out in various formats. The precision (number of decimal places) of the figures printed out and reproduced in this report reflects the toxicologically relevant precision in all cases. Deviations between manually calculated and computer-determined figures can thus arise due to rounding. A "zero" number of decimal places does not necessarily represent the pertinent measurement precision of the detection system. Pulmonary function data are archived and presented in raw data without any post-processing. The post-processing employed in the respective summary figures in the result section and in the Appendix used different low-pass filters, i.e., averaged data may differ slightly in their appearance.

7.19. Archiving the raw data and the report

The study protocol, raw data, specimens and the final report are retained in archives specified by Toxicology of Bayer AG. The storage of a retention sample of the test item and, if applicable, also of the reference items is in the responsibility of the sponsor.

8. RESULTS

8.1. Generation and Characterization of Atmosphere

Technical information concerning generation of test atmospheres is provided in Table 1.

Table 1: Generation and chamber conditions

	Group 1	Group 2	Group 3	Group 4	Group 5
Target Conc. (mg/m ³)	0	2	10	50	100
Nominal Conc. (mg/m ³)	Control (air)	52	52	193	502
Test substance (μl/min)	0	10	10	10	15
Temperature of nozzle (°C)	23 ^a	23 ^a	50	50	50
Gravimetric Conc. (mg/m ³)	--	0.8	12.7	37.3	95
Analytical Conc. (mg/m ³)	--	3.9	15.5	37.8	96.6
Primary Inlet Air Flow (l/min)	15	15	15	15	15
1. Dilution Exhaust Air Flow (l/min)	10	10	10	7.5	2
1. Dilution Inlet Air Flow (l/min)	25	25	25	22.5	17
2. Dilution Exhaust Air Flow (l/min)	18	18	18	--	--
2. Dilution Inlet Air Flow (l/min)	18	18	18	--	--
Exhaust Air Flow (l/min)	27	27	27	27	27
Temperature (mean, °C)	22.8	23.1	23.1	23.1	22.8
Rel. Humidity (mean, %)	15.1	15.7	15.1	16.0	16.0
MMAD (μm)	--	1.12	1.15	1.17	1.23
GSD	--	1.63	1.50	1.50	1.50
Aerosol Mass < 3 μm (%)	--	97.9	99.1	99.1	98.7
Mass recovered (mg/m ³)	--	1.41	12.07	41.83	100.69

MMAD = Mass Median Aerodynamic Diameter. GSD = Geometric Standard Deviation. -- = not applicable. For calculation of mass related nominal concentration a specific density of 1.16 g/ml was used. a) Assumed to be similar as inhalation chamber temperature. Dilution of primary atmosphere: see Fig. 1 for details.

For specific information concerning calculations of aerosol MMAD, GSD, and mass dependent size fraction below 3 μm, see the Appendix.

Characterization of the test atmospheres: Analytical and real-time aerosol monitoring of the test atmosphere from the breathing zone (for details see Appendix) indicated that the exposure conditions were temporally stable over the exposure period. The comparison of concentrations obtained by gravimetric analysis (filter and cascade impactor analyses) demonstrate that both determinations provided virtually identical results. Results obtained by the gravimetric method, when compared with

the analytical method, demonstrated a lower concentration in group 2 whilst in the remaining groups both methods provided almost identical results. It appears that the difference of the gravimetric and nitro-reagent methods at the lower concentration is related to the lower limit of quantification of the filter method.. Experimental evidence suggests, that the particle-size distribution is adequate for acute inhalation toxicity studies (SOT, 1992, OPPTS, 1998). Thus, the results of the characterization of test atmospheres are conclusive and there was no evidence of interstage wall-losses (cascade impactor) or sampling errors.

Temperature value of the inhalation chamber exposure atmosphere were in the range suggested by the testing guidelines. Humidity was lower than recommended by the testing guidelines due to the dry air used for the dispersion of the test substance.

8.2. Toxicological Results

The results obtained during and after exposures of four male rats and four male mice per group for approximately 3-h to the aerosolized test substance are summarized in Table 2 and 3, respectively.

Table 2: Summary of acute inhalation toxicity and physiological data - Mice

N Group /sex	Target Concentration (mg/m ³)	Toxicological Result	Onset and Duration of Signs	Onset of Mortality
1 / m	0	0 / 0 / 4	--	--
2 / m	2	0 / 0 / 4	--	--
3 / m	10	0 / 3 / 4	0d	--
4 / m	50	0 / 3 / 4	0d	--
5 / m	100	2 / 4 / 4	0d - 1d	1d

Values given in the 'Toxicological results' column are:

1st = number of dead animals.

2nd = number of animals with signs after cessation of exposure

3rd = number of animals exposed.

Table 3: Summary of acute inhalation toxicity and physiological data - Rats

N Group /sex	Target Concentration (mg/m ³)	Toxicological Result	Onset and Duration of Signs	Onset of Mortality
1 / m	0	0 / 0 / 4	--	--
2 / m	2	0 / 0 / 4	--	--
3 / m	10	0 / 0 / 4	--	--
4 / m	50	0 / 0 / 4	--	--
5 / m	100	0 / 4 / 4	0d - 1d	--

Values given in the 'Toxicological results' column are:

1st = number of dead animals.

2nd = number of animals with signs after cessation of exposure

3rd = number of animals exposed.

Observations and signs

Details concerning signs and observations are provided in the Appendix in the form of various incidence tables. The following list of signs is focusing on toxicologically significant signs only.

Group 1-4: All rats tolerated the exposure without specific effects. Mice of groups 3 and 4 experienced an irregular breathing pattern.

Group 5: All mice displayed a reduced motility, labored breathing pattern on the exposure day. Rats displayed a reduced motility, labored breathing pattern, tachypnea and ungroomed hair-coat. Two out of four mice died up to the first postexposure day.

Evaluation of sensory irritation potential

The evoked changes on breathing patterns resemble those known to occur following exposure to '*lower respiratory tract sensory irritants*', since during the exposure period a characteristic apneic period (cf. Fig. 5) between the breaths rather than a bradypneic period between end-expiration and start of inspiration has occurred.

As illustrated in Figs. 6 to 9 (rats) and 10 to 13 (mice) the relative change in breathing patterns are indicative of a shallower, and to some extent also high frequent type of breathing pattern. The respective changes were observed in mice as well as in rats, however, appeared to be markedly more pronounced in mice when

compared with rats. Due to this mode of action (lower respiratory tract irritation), a calculation of a RD_{50} -concentration was not attempted.

Figure 5: Inspiration: positive flow, expiration: negative flow, upper curve: flow, lower curve: volume. Volume is digitally derived from the flow signal. The flow algorithm derived tick marks (lower panel) are placed at the (a) start and (b) end of inspiration and (c) end of expiration. The apnea time is defined as the time elapsed from end of expiration to the start of inspiration (c-d). x-axis ticks: 200 msec.

a) Breathing pattern following exposure to a lower respiratory tract irritant

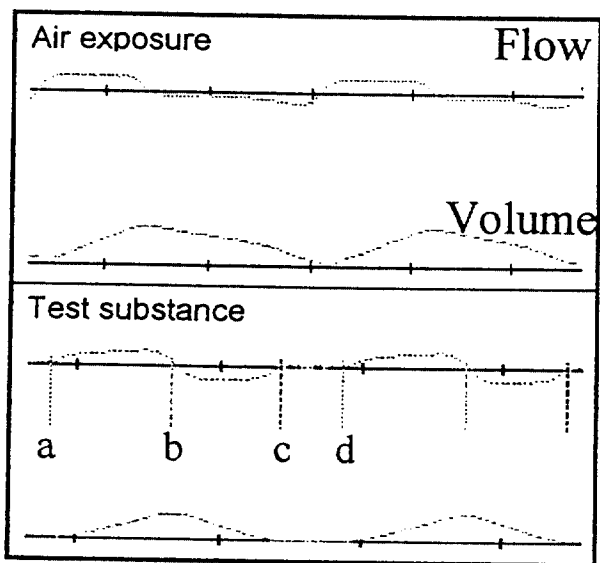


Figure 6: Analysis of concentration-dependence of tidal volume. After acclimatization the rats (n = 4) were exposed for ca. 15-min to air (collection of base-line data). Subsequently the rats were exposed to the aerosolized test substance for ca. 3-h. Data were averaged for time periods of 45-sec.

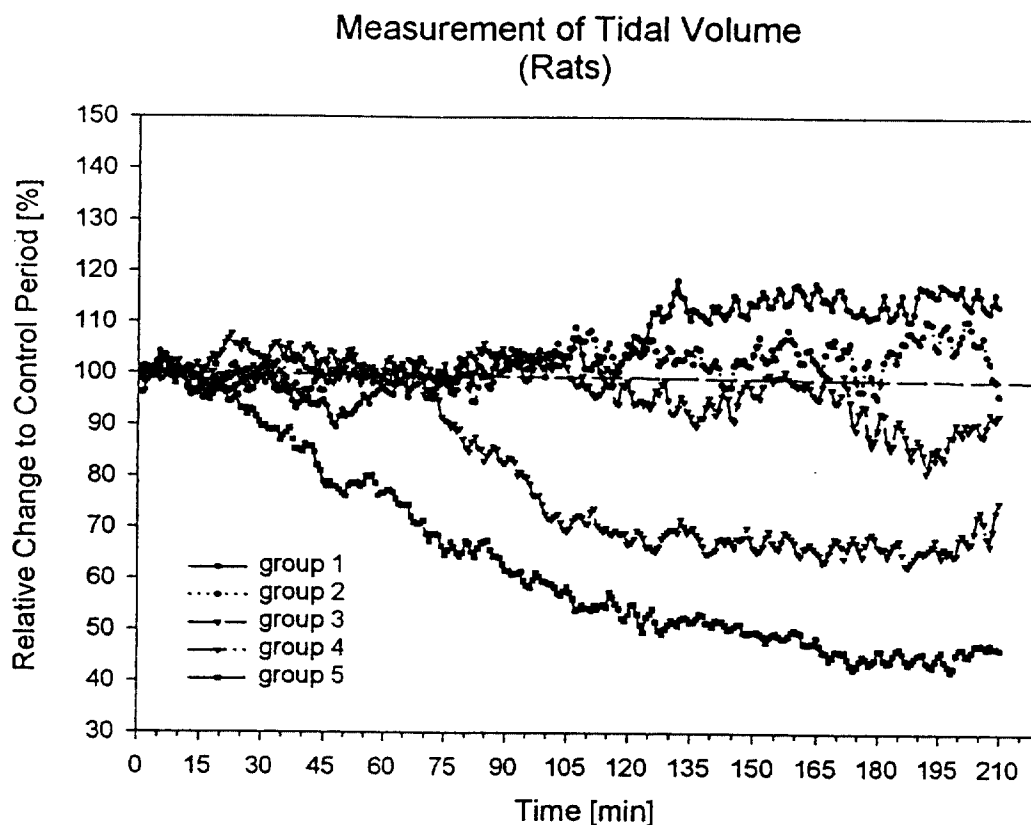


Figure 7: Analysis of concentration-dependence of respiratory rate. After acclimatization the rats ($n = 4$) were exposed for ca. 15-min to air (collection of base-line data). Subsequently the rats were exposed to the aerosolized test substance for ca. 3-h. Data were averaged for time periods of 45-sec.

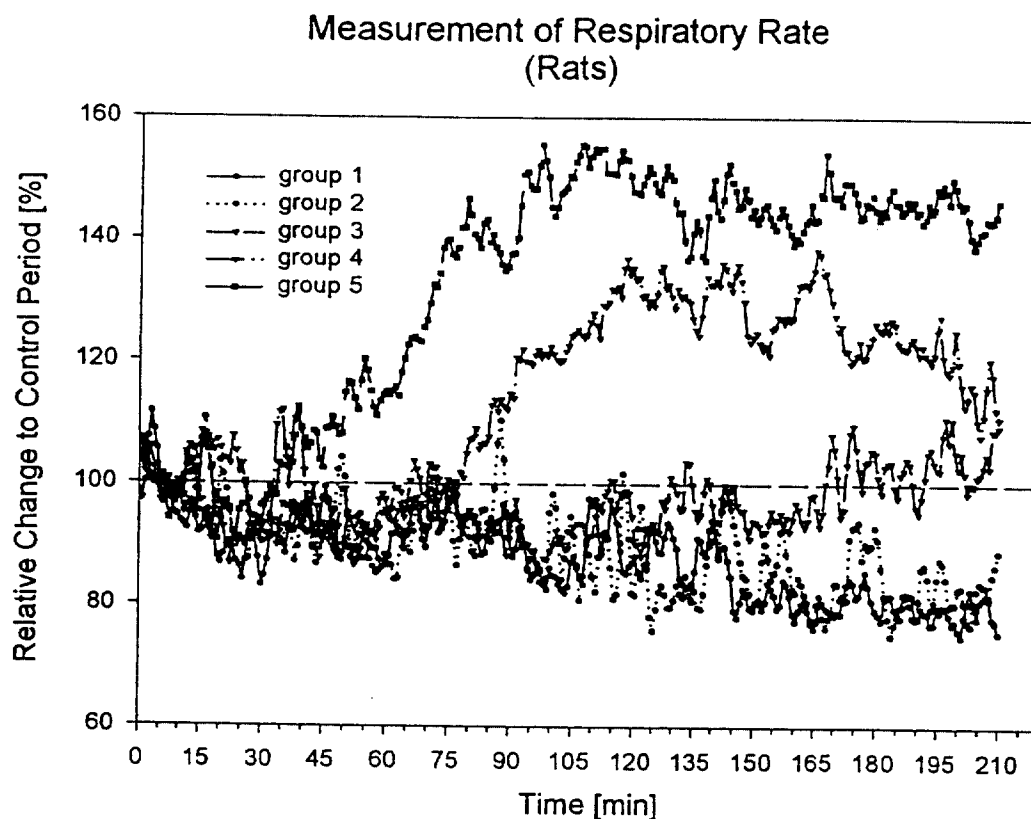


Figure 8: Analysis of concentration-dependence of apnea time. After acclimatization the rats ($n = 4$) were exposed for ca. 15-min to air (collection of base-line data). Subsequently the rats were exposed to the aerosolized test substance for ca. 3-h. Data were averaged for time periods of 45-sec.

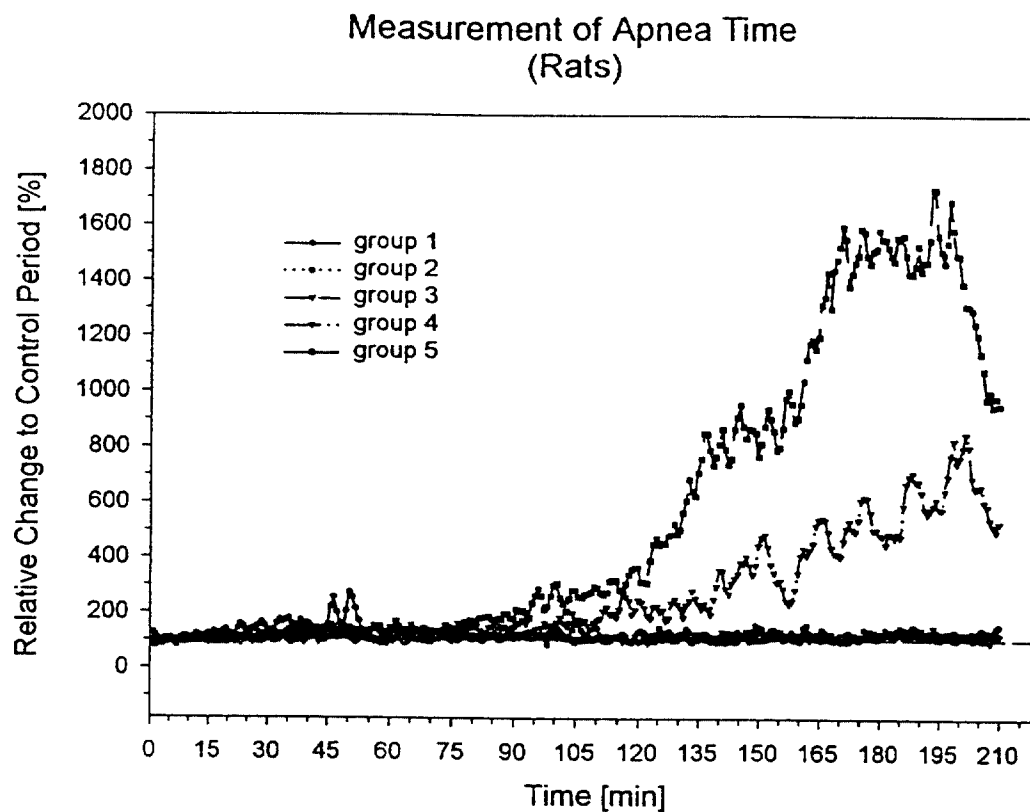


Figure 9: Analysis of concentration-dependence of respiratory minute volume. After acclimatization the rats ($n = 4$) were exposed for ca. 15-min to air (collection of base-line data). Subsequently the rats were exposed to the aerosolized test substance for ca. 3-h. Data were averaged for time periods of 45-sec.

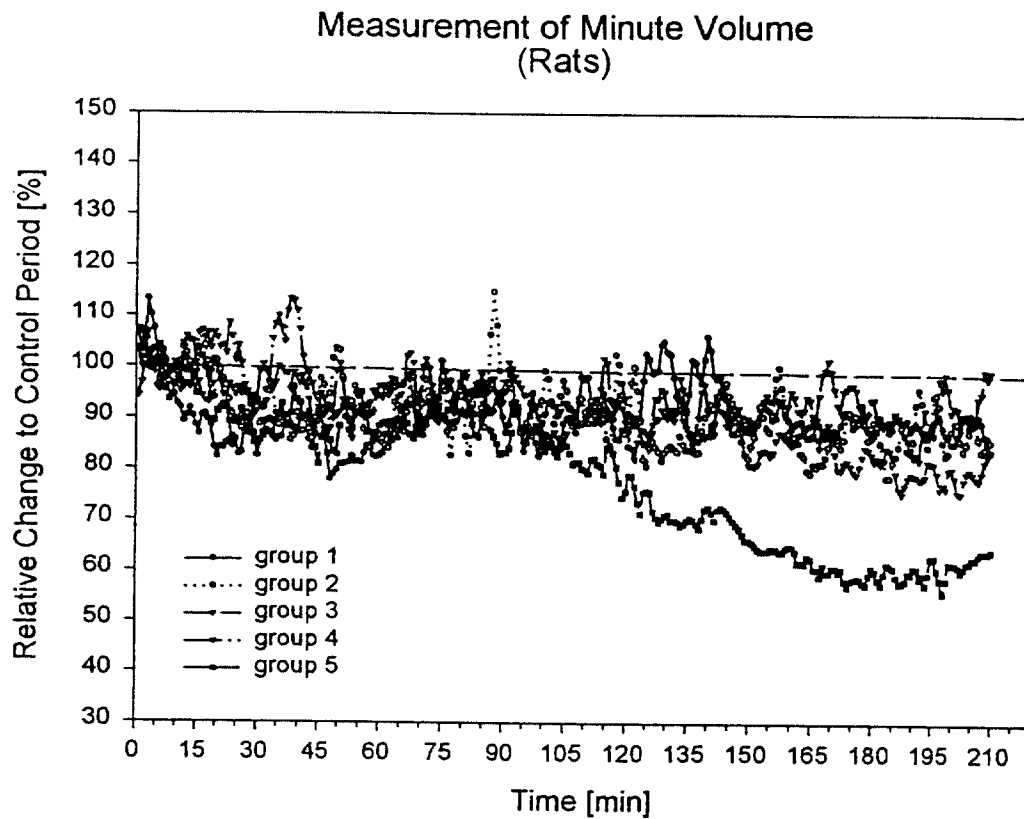


Figure 10: Analysis of concentration-dependence of tidal volume. After acclimatization the mice (n = 4) were exposed for ca. 15-min to air (collection of base-line data). Subsequently the rats were exposed to the aerosolized test substance for ca. 3-h. Data were averaged for time periods of 45-sec.

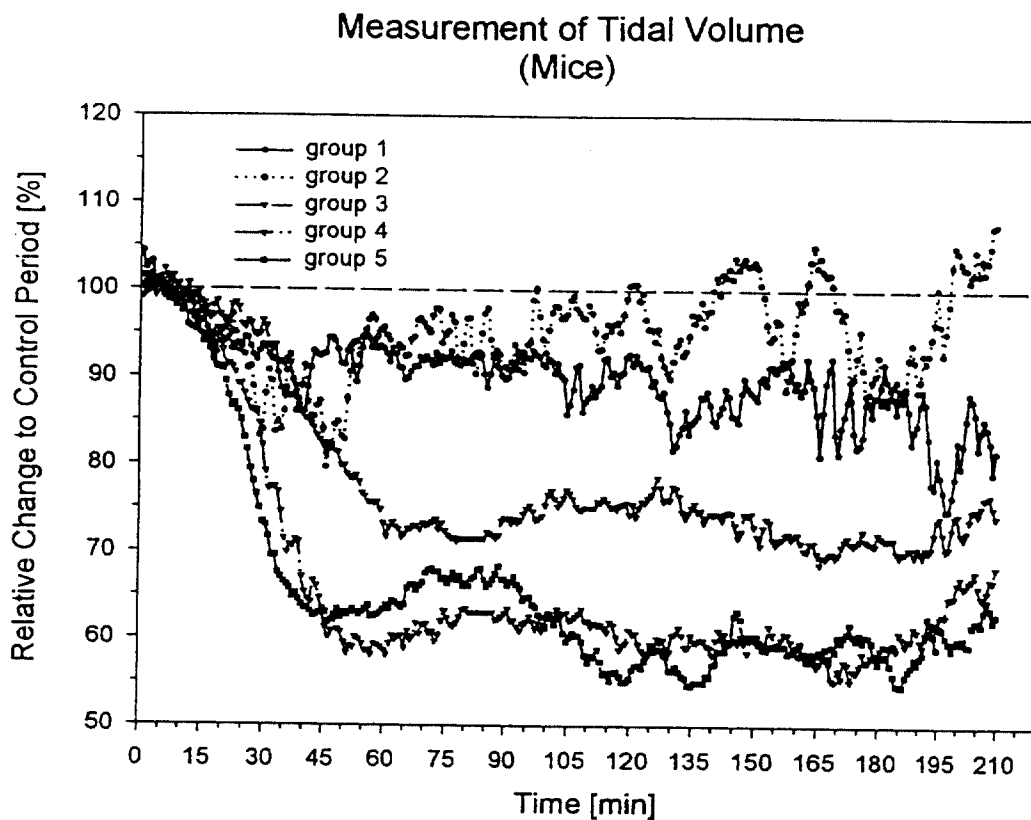


Figure 11: Analysis of concentration-dependence of respiratory rate. After acclimatization the mice ($n = 4$) were exposed for ca. 15-min to air (collection of base-line data). Subsequently the rats were exposed to the aerosolized test substance for ca. 3-h. Data were averaged for time periods of 45-sec.

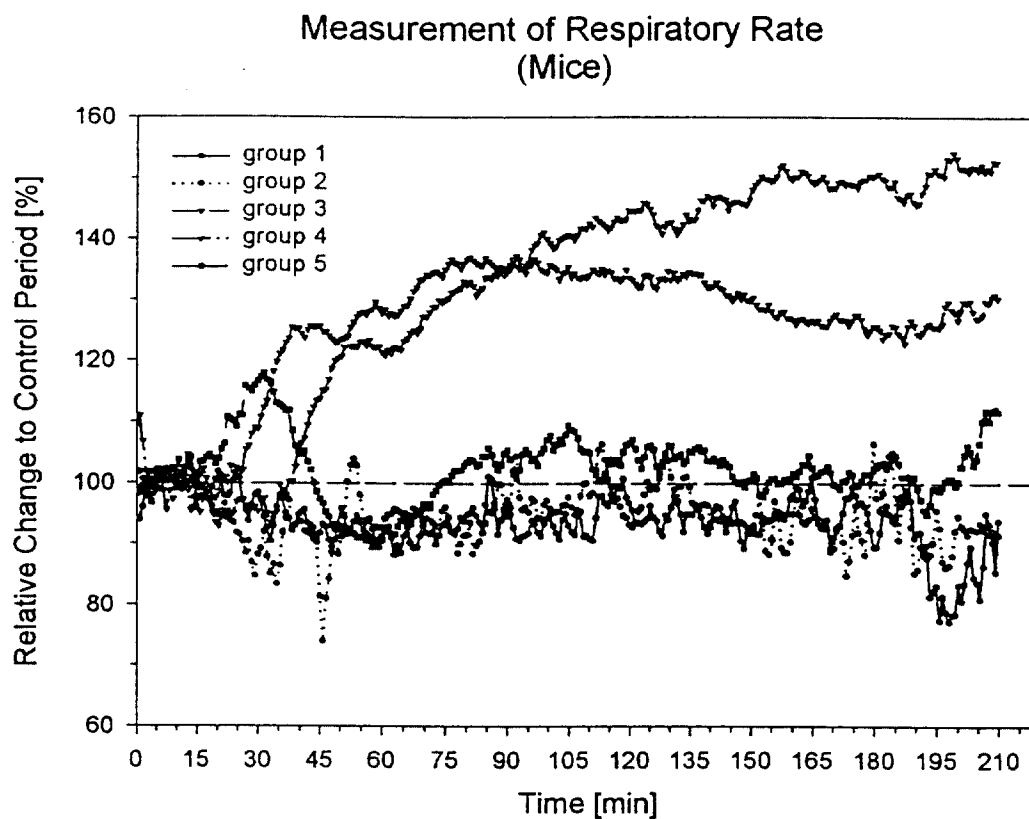


Figure 12: Analysis of concentration-dependence of respiratory minute volume. After acclimatization the mice (n = 4) were exposed for ca. 15-min to air (collection of base-line data). Subsequently the rats were exposed to the aerosolized test substance for ca. 3-h. Data were averaged for time periods of 45-sec.

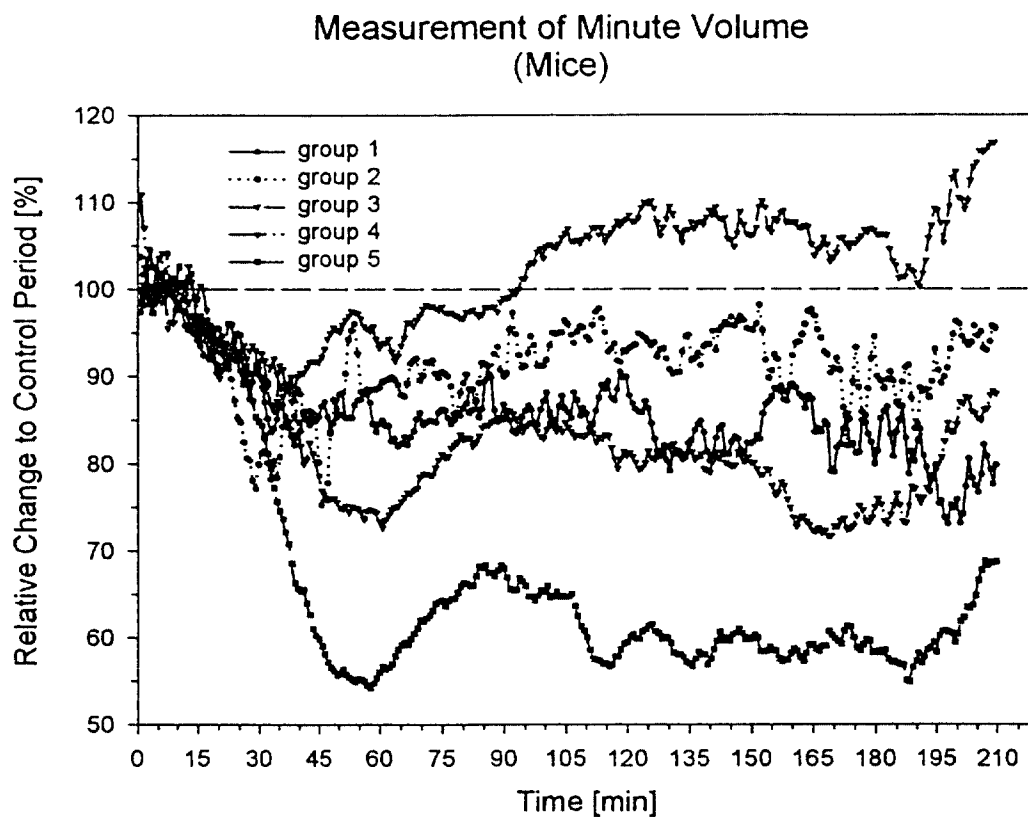
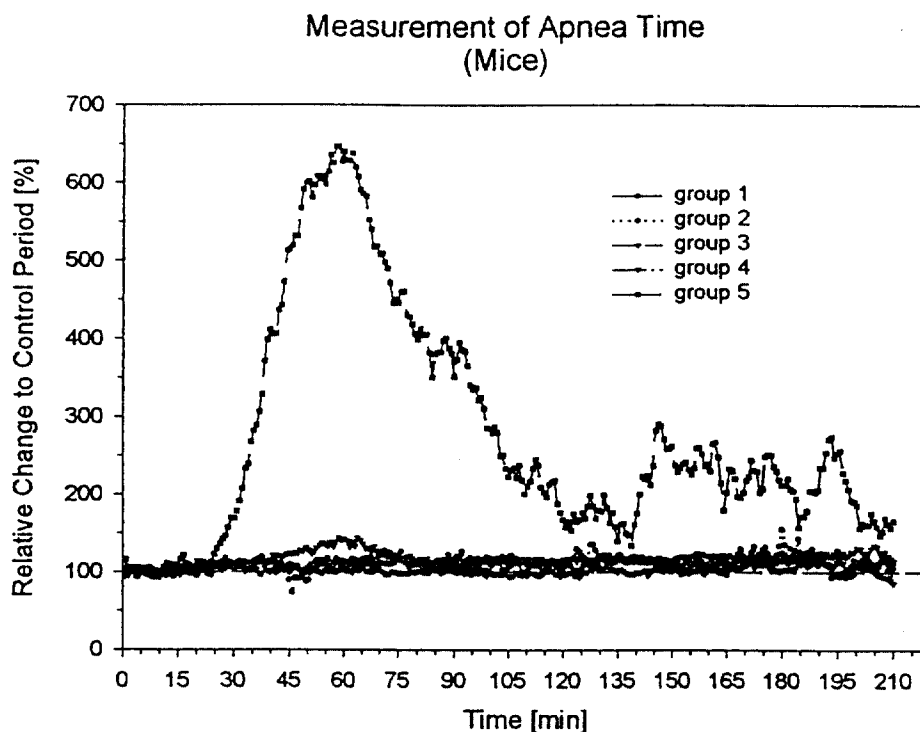


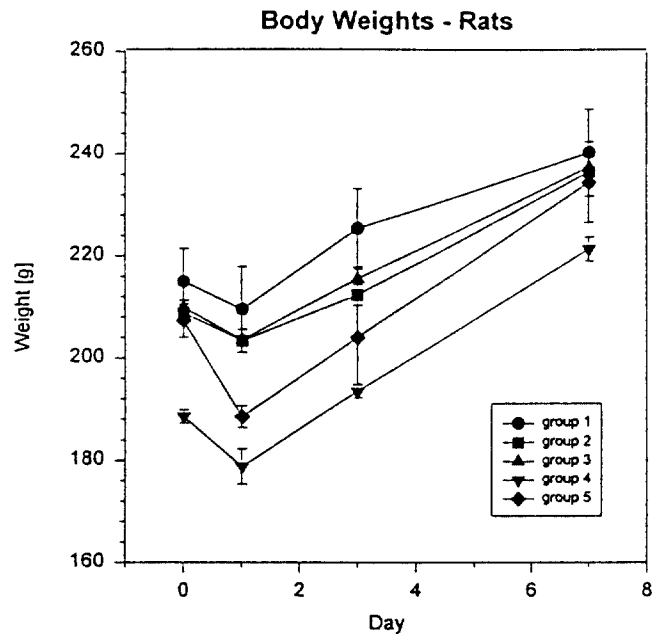
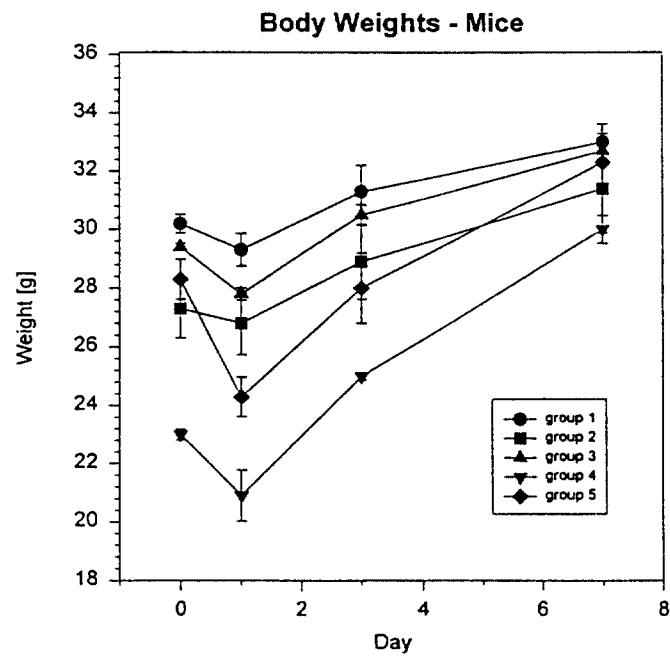
Figure 13: Analysis of concentration-dependence of apnea time. After acclimatization the mice (n = 4) were exposed for ca. 15-min to air (collection of baseline data). Subsequently the rats were exposed to the aerosolized test substance for ca. 3-h. Data were averaged for time periods of 45-sec.



Based on the most sensitive end-point (change of tidal volume in mice) a concentration of 3.9 mg/m³ (group 2) has been tolerated without appreciable effects whereas 15.5 mg/m³ demonstrate first signs of lower respiratory tract irritation.

Body weights

Results of the evaluation of the body weights are included in the Appendix. Comparisons between control animals with those in the groups exposed to the test substance revealed transient effects on body weight gains in groups 4 and 5. The changes observed in group 5 (rats) gained statistical significance. Remaining statistical significant changes are considered to be of no toxicological relevance. The overall change of mean body weights is depicted in Figs. 14 and 15 for rats and mice, respectively.

Figure 14: Body Weights (means \pm standard deviation) - Rats**Figure 15: Body Weights (means \pm standard deviation) - Mice**

Necropsy

Individual findings from the gross-pathological examinations are summarized in the Appendix. A qualitative description, only of findings of toxicological importance and for toxicological evaluation, is given below.

Animals sacrificed at the end of the observation period: In rats and mice exposed to the test compound a conclusive, concentration-dependent increased incidence of macroscopic findings could not be ascertained up to and including group 4. In rats of group 5 the following changes were observed: lungs with red foci and less collapsed. Surviving mice were unobtrusive

Mice that died intercurrently: Mice that died up to the first postexposure day showed dark-red and less collapsed lung with white, foamy content in trachea (lung edema).

9. EVALUATION AND DISCUSSION

A study focusing on the acute respiratory tract sensory irritation potency of DESMODUR VP LS 2294 has been conducted in young adult male rats and mice. With regard to the intensity of changes of breathing patterns as well as clinical findings, mice appeared to be more sensitive than rats. Therefore, in compliance with the ASTM (1984) method, toxicological assessment is focusing on the results obtained with mice.

With regard to the intensity of changes of breathing patterns as well as clinical findings, mice appeared to be more sensitive than rats. Therefore, toxicological assessment is focusing on the results obtained with mice. 3.9 mg/m³ air was tolerated without any clinical sings, changes on body weights or appreciable effects on breathing patterns. Mice exposed to the next higher concentration (15.5 mg/m³) elicited an irregular breathing pattern and a concentration-dependent decrease in tidal volume. An increase in respiratory rate was seen at concentrations of 15.5 and 37.8 mg/m³ whereas the increase in respiratory rate during exposure to 96.6 mg/m³ was transient and became normal during the course of exposure. Mortality (50%) occurred in mice exposed to 96.6 mg/m³. An apparent relationship of lung edema formation and mortality was observed.

In the present study, it is observed that the respirable aerosol of DESMODUR VP LS 2294 caused an apneic pause between end of expiration and inspiration and a concentration-dependent decrease in tidal volume, however, without conclusive, i.e., concentration-dependent changes in respiratory rate. Marked exposure-duration related exacerbation of effects could not be ascertained during the 3-h exposure period. The shallow(er) breathing pattern as a response to DESMODUR VP LS 2294-aerosol exposure is thought to be caused by a vagally mediated reflex originating from the stimulation of pulmonary C fibers. The change in respiratory patterns thus indicate that this effect is dominated by the stimulation of receptors located in the lower- rather than upper-respiratory tract.

Due to this mode of action (lower respiratory tract irritation), a calculation of a RD₅₀-concentration was not attempted. The non-irritant threshold concentration is considered to be 3.9 mg/m³ air.

10. KEY TO ABBREVIATIONS

Konz.	Concentration
nomin.	Nominal
analyt.	Analytical
mcm/ μ m	Micrometer
Expos.	Exposure
L/min	liter/minute
MMAD	Mass Median Aerodynamic Diameter
NMAD	Number Median Aerodynamic Diameter
GSD	Geometric standard deviation (GSD)
ECD	Effective cut-off diameter
STAND, S, Std, s	Standard deviation (σ) (STD)
MW/MEANS	Means
F	F-test value (F-ratio)
DF	Degrees of freedom
PROB	Probability
SS	Total sum of squares
MS	Mean squares
TREATMENT	- between the groups
ERROR	- within the groups
TOTAL	- total

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12. APPENDIX

Test compound / concentration of atmospheres

Group	Date	Volume sampled (l)	Animal Nos.	Target Concentration (mg/m ³)	Analytical Concentration (mg/m ³)	Gravimetric Concentration (mg/m ³)
1	09.10.1998	--	1-4	air control	--	--
2	08.10.1998	195 ^a / 250 ^b	17-20	2	3.88 ^c	0.8 ^d
3	07.10.1998	50 / 150	13-16	10	15.5	12.7
4	02.10.1998	30 / 110	5-8	50	37.8	37.3
5	05.10.1998	20 / 40	9-12	100	96.6	95

-- = not determined, a) Analysis of test substance, sampling flow rate: 1 l/min; b) Filter analysis, sampling flow rate: 4 l/min; c) Analysis of test substance using the analytical described in Appendix, d) Analysis of test substance by filter samples

Particle-size Characterization of Test Atmosphere

Group	Date of exposure (DD.MM.YY)	Target Concentrations (mg/m ³ air)	MMAD [μm]	GSD	Mass ≤ 3 μm [%]	Concentration (mg/m ³ air)
2	08.10.1998	2	1.12	1.63	97.9	1.41
3	07.10.1998	10	1.15	1.50	99.1	12.1
4	02.10.1998	50	1.17	1.50	99.1	41.8
5	05.10.1998	100	1.21	1.49	98.9	98.0
			1.24	1.50	98.5	103.4

All measurements represent cascade impactor analyses.

Representative examples of evaluation of particle-size distributions for each group are provided on the next pages.

Characterization of Particle Size Distribution**ANALYSIS OF PARTICLE DISTRIBUTIONS**

Type of investigation: Acute Inhalation - Aerosol

Compound: Desmodur VP LS 2294

Date of exposure: 08.10.98

Study-no.: T3067460

Target concentration: 2.0 mg/m3 air

N	Impactor stage (um - um)	Cut-Off diameter (um)	Mass/ stage (mg)	Rel. mass (%)	Cumul. mass (%)
1	.06 - .12	.060	.000	.00	.00
2	.12 - .25	.120	.001	.14	.00
3	.25 - .49	.250	.034	4.59	.14
4	.49 - .90	.490	.181	24.46	4.73
5	.90 - 1.85	.900	.448	60.54	29.19
6	1.85 - 3.69	1.850	.068	9.19	89.73
7	3.69 - 7.42	3.690	.004	.54	98.92
8	7.42 -14.80	7.420	.004	.54	99.46
9	14.80 -30.00	14.800	.000	.00	100.00

Mass Median Aerodynamic Diameter (MMAD): 1.12 um
 Geometric standard deviation (GSD): 1.63
 Number Median Aerodynamic Diameter (NMAD): .54 um
 Surface Median Aerodynamic Diameter (SMAD): .88 um

System: BERNER-IMPACTOR I

Air flow:

5.85 liter/min.

Sampling time:

5400.00 seconds

Concentration (computed):

1.41 mg/m3 air

Respirability (percent < 1.0 um):

1. Mass related: 41.3 % (measured)
2. Number related: 89.3 % (extrapolated)

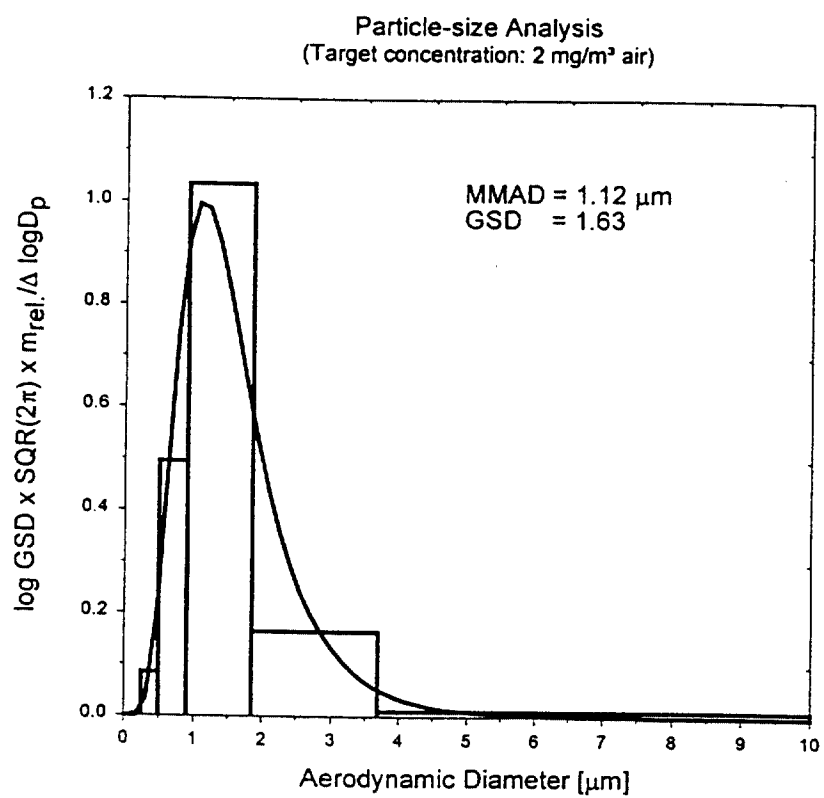
Respirability (percent < 3.0 um):

1. Mass related: 97.9 % (measured)
2. Number related: 99.1 % (extrapolated)

Respirability (percent < 5.0 um):

1. Mass related: 99.1 % (measured)
2. Number related: 99.1 % (extrapolated)

ECD-definition: right cut-size (Dp+1)



ANALYSIS OF PARTICLE DISTRIBUTIONS

Type of investigation: Acute Inhalation - Aerosol

Compound: Desmodur VP LS 2294

Date of exposure: 07.10.98

Study-no.: T3067460

Target concentration: 10.0 mg/m3 air

N	Impactor stage (um - um)	Cut-Off diameter (um)	Mass/ stage (mg)	Rel. mass (%)	Cumul. mass (%)
1	.06 - .12	.060	.000	.00	.00
2	.12 - .25	.120	.005	.12	.00
3	.25 - .49	.250	.080	1.89	.12
4	.49 - .90	.490	.938	22.14	2.01
5	.90 - 1.85	.900	2.724	64.29	24.14
6	1.85 - 3.69	1.850	.471	11.12	88.44
7	3.69 - 7.42	3.690	.012	.28	99.55
8	7.42 - 14.80	7.420	.007	.17	99.83
9	14.80 - 30.00	14.800	.000	.00	100.00

Mass Median Aerodynamic Diameter (MMAD): 1.15 um
 Geometric standard deviation (GSD): 1.50
 Number Median Aerodynamic Diameter (NMAD): .70 um
 Surface Median Aerodynamic Diameter (SMAD): .98 um

System: BERNER-IMPACTOR I

Air flow: 5.85 liter/min.

Sampling time: 3600.00 seconds

Concentration (computed): 12.07 mg/m3 air

Respirability (percent < 1.0 um):

- 1. Mass related: 36.3 % (measured)
- 2. Number related: 80.5 % (extrapolated)

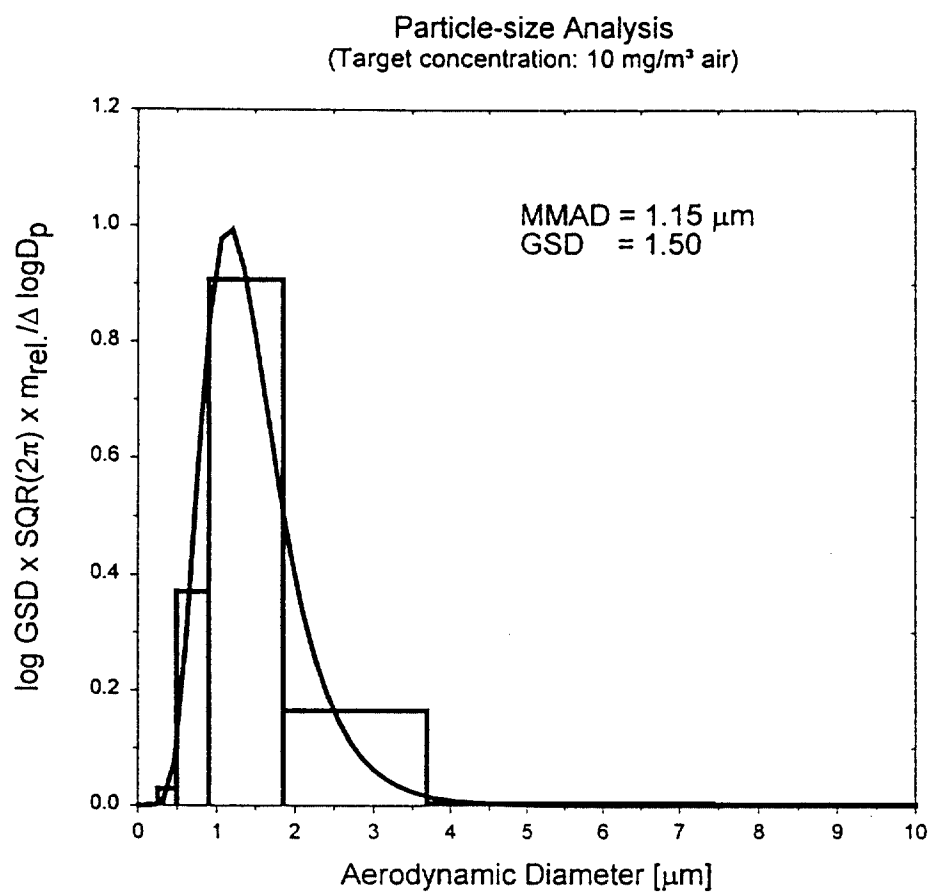
Respirability (percent < 3.0 um):

- 1. Mass related: 99.1 % (measured)
- 2. Number related: 99.1 % (extrapolated)

Respirability (percent < 5.0 um):

- 1. Mass related: 99.1 % (measured)
- 2. Number related: 99.1 % (extrapolated)

ECD-definition: right cut-size (Dp+1)



ANALYSIS OF PARTICLE DISTRIBUTIONS

Type of investigation: Acute Inhalation - Aerosol

Compound: Desmodur VP LS 2294

Date of exposure: 2.10.98

Study-no.: T3067460

Target concentration: 50.0 mg/m3 air

N	Impactor stage (um - um)	Cut-Off diameter (um)	Mass/ stage (mg)	Rel. mass (%)	Cumul. mass (%)
1	.06 - .12	.060	.001	.03	.00
2	.12 - .25	.120	.003	.08	.03
3	.25 - .49	.250	.066	1.80	.11
4	.49 - .90	.490	.782	21.30	1.91
5	.90 - 1.85	.900	2.370	64.56	23.21
6	1.85 - 3.69	1.850	.440	11.99	87.77
7	3.69 - 7.42	3.690	.007	.19	99.75
8	7.42 - 14.80	7.420	.002	.05	99.95
9	14.80 - 30.00	14.800	.000	.00	100.00

Mass Median Aerodynamic Diameter (MMAD): 1.17 um

Geometric standard deviation (GSD): 1.50

Number Median Aerodynamic Diameter (NMAD): .71 um

Surface Median Aerodynamic Diameter (SMAD): .99 um

System: BERNER-IMPACTOR I

Air flow: 5.85 liter/min.

Sampling time: 900.00 seconds

Concentration (computed): 41.83 mg/m3 air

Respirability (percent < 1.0 um):

1. Mass related: 35.3 % (measured)
2. Number related: 79.9 % (extrapolated)

Respirability (percent < 3.0 um):

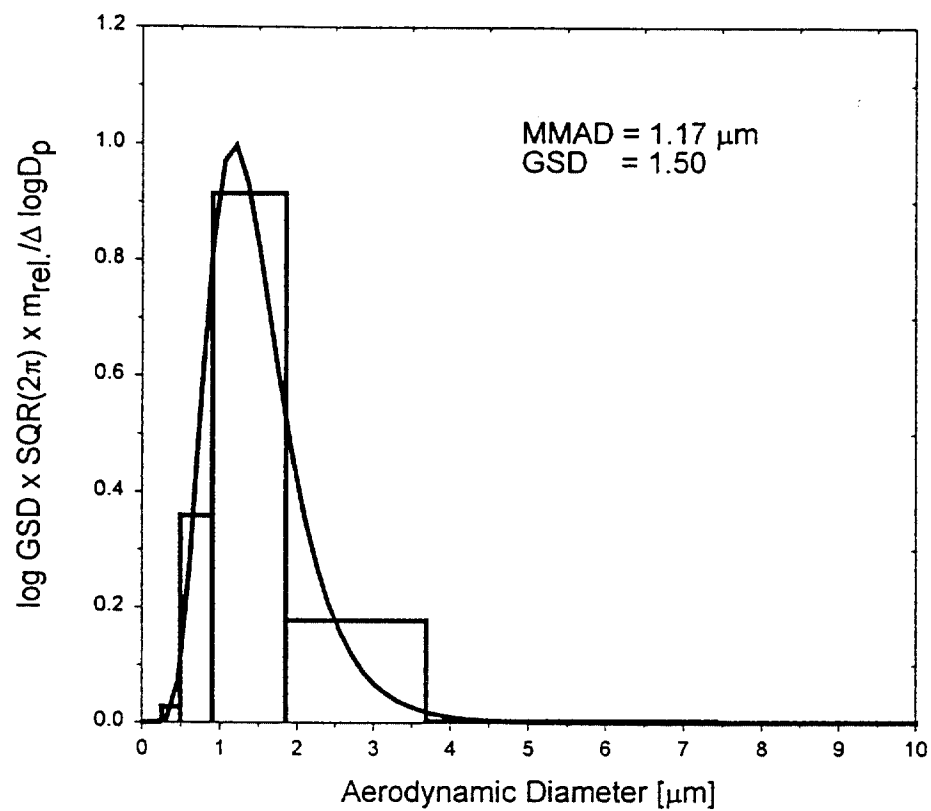
1. Mass related: 99.1 % (measured)
2. Number related: 99.1 % (extrapolated)

Respirability (percent < 5.0 um):

1. Mass related: 99.1 % (measured)
2. Number related: 99.1 % (extrapolated)

ECD-definition: right cut-size (Dp+1)

Particle-size Analysis
(Target concentration: 50 mg/m³ air)



ANALYSIS OF PARTICLE DISTRIBUTIONS

Type of investigation: Acute Inhalation - Aerosol

Compound: Desmodur VP LS 2294

Date of exposure: 5.10.98

Study-no.: T3067460

Target concentration: 100.0 mg/m3 air

N	Impactor stage (um - um)	Cut-Off diameter (um)	Mass/ stage (mg)	Rel. mass (%)	Cumul. mass (%)
1	.06 - .12	.060	.000	.00	.00
2	.12 - .25	.120	.001	.02	.00
3	.25 - .49	.250	.079	1.31	.02
4	.49 - .90	.490	1.087	17.98	1.32
5	.90 - 1.85	.900	3.957	65.45	19.30
6	1.85 - 3.69	1.850	.900	14.89	84.75
7	3.69 - 7.42	3.690	.013	.22	99.64
8	7.42 - 14.80	7.420	.009	.15	99.85
9	14.80 - 30.00	14.800	.000	.00	100.00

Mass Median Aerodynamic Diameter (MMAD): 1.24 um
 Geometric standard deviation (GSD): 1.50
 Number Median Aerodynamic Diameter (NMAD): .75 um
 Surface Median Aerodynamic Diameter (SMAD): 1.05 um

System: BERNER-IMPACTOR I

Air flow:

5.85 liter/min.

Sampling time:

600.00 seconds

Concentration (computed):

103.35 mg/m3 air

Respirability (percent < 1.0 um):

1. Mass related: 30.3 % (measured)
2. Number related: 75.7 % (extrapolated)

Respirability (percent < 3.0 um):

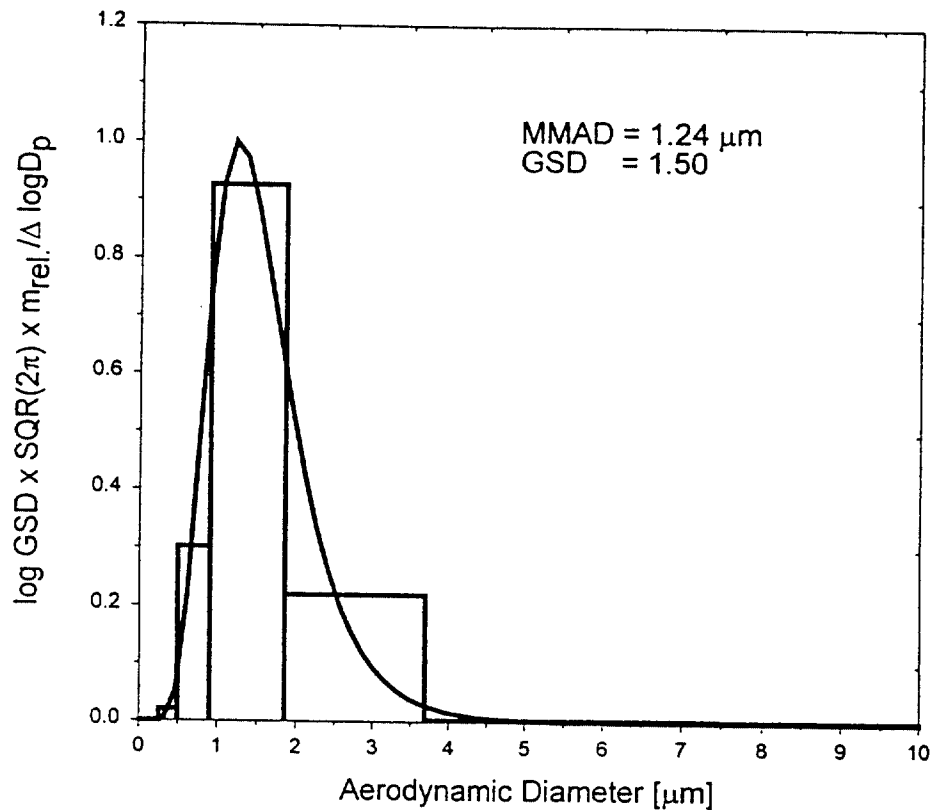
1. Mass related: 98.5 % (measured)
2. Number related: 99.1 % (extrapolated)

Respirability (percent < 5.0 um):

1. Mass related: 99.1 % (measured)
2. Number related: 99.1 % (extrapolated)

ECD-definition: right cut-size (Dp+1)

Particle-size Analysis
(Target concentration: 100 mg/m³ air)



Body weights - Rats

Desmodur VP LS 2294 / T3067460

Analysis of Body Weights [all data in g]

Group 1: 0 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
1	218.	214.	226.	243.
2	213.	204.	221.	232.
3	207.	201.	218.	235.
4	222.	219.	236.	251.
MEAN	215.0	209.5	225.3	240.3
STD	6.5	8.4	7.9	8.5

Group 2: 2 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
17	209.	204.	214.	239.
18	211.	205.	214.	239.
19	208.	200.	210.	234.
20	207.	204.	211.	234.
MEAN	208.8	203.3	212.3	236.5
STD	1.7	2.2	2.1	2.9

Group 3: 10 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
13	211.	203.	215.	236.
14	208.	204.	214.	238.
15	211.	204.	214.	234.
16	209.	203.	219.	242.
MEAN	209.8	203.5	215.5	237.5
STD	1.5	.6	2.4	3.4

Group 4: 50 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
5	190.	180.	194.	221.
6	187.	175.	193.	223.
7	189.	183.	195.	223.
8	188.	177.	192.	218.
MEAN	188.5	178.8	193.5	221.3
STD	1.3	3.5	1.3	2.4

Group 5: 100 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
9	203.	186.	191.	224.
10	208.	191.	211.	239.
11	207.	188.	205.	233.
12	211.	189.	209.	242.
MEAN	207.3	188.5	204.0	234.5
STD	3.3	2.1	9.0	7.9

Desmodur VP LS 2294 / T3067460

Analysis of Body Weight Gains [all data in g]

Group 1: 0 mg/m³ - MALES

	Postexposure Day		
	1	3	7
1	-4.00	12.00	17.00
2	-9.00	17.00	11.00
3	-6.00	17.00	17.00
4	-3.00	17.00	15.00
MEAN	-5.5	15.8	15.0
STD	2.6	2.5	2.8

Group 2: 2 mg/m³ - MALES

	Postexposure Day		
	1	3	7
17	-5.00	10.00	25.00
18	-6.00	9.00	25.00
19	-8.00	10.00	24.00
20	-3.00	7.00	23.00
MEAN	-5.5	9.0	24.3
STD	2.1	1.4	1.0

Group 3: 10 mg/m³ - MALES

	Postexposure Day		
	1	3	7
13	-8.00	12.00	21.00
14	-4.00	10.00	24.00
15	-7.00	10.00	20.00
16	-6.00	16.00	23.00
MEAN	-6.3	12.0	22.0
STD	1.7	2.8	1.8

Group 4: 50 mg/m³ - MALES

	Postexposure Day		
	1	3	7
5	-10.00	14.00	27.00
6	-12.00	18.00	30.00
7	-6.00	12.00	28.00
8	-11.00	15.00	26.00
MEAN	-9.8	14.8	27.8
STD	2.6	2.5	1.7

Group 5: 100 mg/m³ - MALES

	Postexposure Day		
	1	3	7
9	-17.00	5.00	33.00
10	-17.00	20.00	28.00
11	-19.00	17.00	28.00
12	-22.00	20.00	33.00
MEAN	-18.8	15.5	30.5
STD	2.4	7.1	2.9

ONE-WAY ANALYSIS OF VARIANCE PROGRAM : ANOVA

Analysis of Day: 1 / MALES

```

Group-no.: 1
  -4.000    -9.000    -6.000    -3.000
MEDIAN=    -5.000  MEAN=    -5.500  STD =    2.646

Group-no.: 2
  -5.000    -6.000    -8.000    -3.000
MEDIAN=    -5.500  MEAN=    -5.500  STD =    2.082

Group-no.: 3
  -8.000    -4.000    -7.000    -6.000
MEDIAN=    -6.500  MEAN=    -6.250  STD =    1.708

Group-no.: 4
  -10.000   -12.000    -6.000   -11.000
MEDIAN=   -10.500  MEAN=    -9.750  STD =    2.630

Group-no.: 5
  -17.000   -17.000   -19.000   -22.000
MEDIAN=   -18.000  MEAN=   -18.750  STD =    2.363

```

BOXs TEST FOR HOMOGENEITY OF VARIANCES AT P=.05000 LEVEL

CALCULATED F	D.F.s	PROBABILITY
.1633	4 & 338.	.9543

HOMOGENEOUS VARIANCES (ONE-TAILED TEST)

ONE-WAY CLASSIFICATION ANALYSIS OF VARIANCE

SOURCE	SS	DF	MS	F	PROB
TREATMENT	510.3	4	127.58	23.846	.000
ERROR	80.25	15	5.3500		
TOTAL	590.5	19			

OVERALL SIGNIFICANCE AT 5.% (ONE-TAILED) LEVEL

GAMES AND HOWELL MODIFICATION OF
TUKEY-KRAMER'S HONESTLY SIGNIFICANT DIFFERENCE TEST
(WITH THE STUDENTIZED RANGE STATISTIC)

GROUPS COMPARED	CALCULATED TEST VALUE	DEGREES OF FREEDOM	PROBABILITY	CONCLUSION

5. % ONE-TAILED TEST				
1 AND 2	.00	6	1.0000	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 2	.00	6	1.0000	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 3	-.67	5	.9864	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 3	.67	5	.9864	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 4	-3.22	6	.2687	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 4	3.22	6	.2687	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 5	-10.56	6	.0015	SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 5	10.56	6	.0015	SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 3	-.79	6	.9769	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 3	.79	6	.9769	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 4	-3.58	6	.2007	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 4	3.58	6	.2007	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 5	-11.90	6	.0005	SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 5	11.90	6	.0005	SIGNIFICANT
5. % ONE-TAILED TEST				
3 AND 4	-3.16	5	.3005	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
3 AND 4	3.16	5	.3005	NOT SIGNIFICANT
5. % ONE-TAILED TEST				

3 AND 5	-12.13	5	.0010	SIGNIFICANT
5. % TWO-TAILED TEST				

3 AND 5	12.13	5	.0010	SIGNIFICANT
5. % ONE-TAILED TEST				

4 AND 5	-7.20	6	.0127	SIGNIFICANT
5. % TWO-TAILED TEST				

4 AND 5	7.20	6	.0127	SIGNIFICANT

ONE-WAY ANALYSIS OF VARIANCE PROGRAM : ANOVA

Analysis of Day: 3 / MALES

```

Group-no.: 1
  12.000    17.000    17.000    17.000
MEDIAN=    17.000  MEAN=    15.750  STD =    2.500

Group-no.: 2
  10.000    9.000    10.000    7.000
MEDIAN=    9.500  MEAN=    9.000  STD =    1.414

Group-no.: 3
  12.000    10.000    10.000    16.000
MEDIAN=    11.000  MEAN=    12.000  STD =    2.828

Group-no.: 4
  14.000    18.000    12.000    15.000
MEDIAN=    14.500  MEAN=    14.750  STD =    2.500

Group-no.: 5
  5.000    20.000    17.000    20.000
MEDIAN=    18.500  MEAN=    15.500  STD =    7.141

```

BOXs TEST FOR HOMOGENEITY OF VARIANCES AT P=.05000 LEVEL

CALCULATED F	D.F.s	PROBABILITY
2.0579	4 & 338.	.0849

HOMOGENEOUS VARIANCES (ONE-TAILED TEST)

ONE-WAY CLASSIFICATION ANALYSIS OF VARIANCE

SOURCE	SS	DF	MS	F	PROB
TREATMENT	132.3	4	33.075	2.250	.112
ERROR	220.5	15	14.700		
TOTAL	352.8	19			

NO OVERALL SIGNIFICANCE AT 5.% (ONE-TAILED) LEVEL
 NO STATISTICAL DIFFERENCE BETWEEN THE GROUPS

ONE-WAY ANALYSIS OF VARIANCE PROGRAM : ANOVA

Analysis of Day: 7 / MALES

```

Group-no.: 1
  17.000    11.000    17.000    15.000
MEDIAN=    16.000 MEAN=    15.000 STD =    2.828

Group-no.: 2
  25.000    25.000    24.000    23.000
MEDIAN=    24.500 MEAN=    24.250 STD =    .957

Group-no.: 3
  21.000    24.000    20.000    23.000
MEDIAN=    22.000 MEAN=    22.000 STD =    1.826

Group-no.: 4
  27.000    30.000    28.000    26.000
MEDIAN=    27.500 MEAN=    27.750 STD =    1.708

Group-no.: 5
  33.000    28.000    28.000    33.000
MEDIAN=    30.500 MEAN=    30.500 STD =    2.887

```

BOXs TEST FOR HOMOGENEITY OF VARIANCES AT P=.05000 LEVEL

CALCULATED F	D.F.s	PROBABILITY
.8933	4 & 338.	.5301

HOMOGENEOUS VARIANCES (ONE-TAILED TEST)

ONE-WAY CLASSIFICATION ANALYSIS OF VARIANCE

SOURCE	SS	DF	MS	F	PROB
TREATMENT	565.3	4	141.32	30.069	.000
ERROR	70.50	15	4.7000		
TOTAL	635.8	19			

OVERALL SIGNIFICANCE AT 5.% (ONE-TAILED) LEVEL

GAMES AND HOWELL MODIFICATION OF
TUKEY-KRAMER'S HONESTLY SIGNIFICANT DIFFERENCE TEST
(WITH THE STUDENTIZED RANGE STATISTIC)

GROUPS COMPARED	CALCULATED TEST VALUE	DEGREES OF FREEDOM	PROBABILITY	CONCLUSION

5. % ONE-TAILED TEST				
1 AND 2	8.76	4	.0156	SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 2	8.76	4	.0156	SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 3	5.88	5	.0436	SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 3	5.88	5	.0436	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 4	10.91	5	.0023	SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 4	10.91	5	.0023	SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 5	10.85	6	.0012	SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 5	10.85	6	.0012	SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 3	-3.09	5	.3161	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 3	3.09	5	.3161	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 4	5.06	5	.0759	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 4	5.06	5	.0759	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 5	5.81	4	.0644	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 5	5.81	4	.0644	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
3 AND 4	6.51	6	.0204	SIGNIFICANT
5. % TWO-TAILED TEST				
3 AND 4	6.51	6	.0204	SIGNIFICANT
5. % ONE-TAILED TEST				

3 AND 5	7.04	5	.0214	SIGNIFICANT
5. % TWO-TAILED TEST				

3 AND 5	7.04	5	.0214	SIGNIFICANT
5. % ONE-TAILED TEST				

4 AND 5	2.32	5	.5344	NOT SIGNIFICANT
5. % TWO-TAILED TEST				

4 AND 5	2.32	5	.5344	NOT SIGNIFICANT

Body weights - Mice

Desmodur VP LS 2294 / M3067460

Analysis of Body Weights [all data in g]

Group 1: 0 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
1	30.1	28.8	30.0	32.5
2	30.1	29.2	31.4	32.7
3	30.7	30.1	32.1	33.0
4	30.0	29.1	31.6	33.9
MEAN	30.2	29.3	31.3	33.0
STD	.3	.6	.9	.6

Group 2: 2 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
17	26.1	27.3	30.1	33.0
18	27.1	26.7	28.6	30.5
19	28.5	27.9	29.6	32.4
20	27.5	25.4	27.2	29.8
MEAN	27.3	26.8	28.9	31.4
STD	1.0	1.1	1.3	1.5

Group 3: 10 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
13	29.5	27.8	30.8	32.8
14	29.2	27.8	30.1	32.4
15	29.4	28.1	30.2	32.7
16	29.4	27.6	30.7	33.0
MEAN	29.4	27.8	30.5	32.7
STD	.1	.2	.4	.2

Group 4: 50 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
5	23.0	20.9	24.9	30.2
6	23.1	22.1	25.0	30.6
7	22.7	20.2	25.1	29.8
8	23.1	20.3	25.2	29.5
MEAN	23.0	20.9	25.0	30.0
STD	.2	.9	.1	.5

Group 5: 100 mg/m³ - MALES

	Postexposure Day			
	0	1	3	7
9	29.3	23.8		
10	28.1	24.1	27.2	31.6
11	27.8	25.1	28.9	33.0
12	28.0			
MEAN	28.3	24.3	28.0	32.3
STD	.7	.7	1.2	1.0

Desmodur VP LS 2294 / M3067460
Analysis of Body Weight Gains [all data in g]

Group 1: 0 mg/m³ - MALES

	Postexposure Day		
	1	3	7
1	-1.30	1.20	2.50
2	-.90	2.20	1.30
3	-.60	2.00	.90
4	-.90	2.50	2.30
MEAN	-.9	2.0	1.8
STD	.3	.6	.8

Group 2: 2 mg/m³ - MALES

	Postexposure Day		
	1	3	7
17	1.20	2.80	2.90
18	-.40	1.90	1.90
19	-.60	1.70	2.80
20	-2.10	1.80	2.60
MEAN	-.5	2.1	2.5
STD	1.3	.5	.5

Group 3: 10 mg/m³ - MALES

	Postexposure Day		
	1	3	7
13	-1.70	3.00	2.00
14	-1.40	2.30	2.30
15	-1.30	2.10	2.50
16	-1.80	3.10	2.30
MEAN	-1.6	2.6	2.3
STD	.2	.5	.2

Group 4: 50 mg/m³ - MALES

	Postexposure Day		
	1	3	7
5	-2.10	4.00	5.30
6	-1.00	2.90	5.60
7	-2.50	4.90	4.70
8	-2.80	4.90	4.30
MEAN	-2.1	4.2	5.0
STD	.8	1.0	.6

Group 5: 100 mg/m³ - MALES

	Postexposure Day		
	1	3	7
9	-5.50		
10	-4.00	3.10	4.40
11	-2.70	3.80	4.10
12			
MEAN	-4.1	3.4	4.3
STD	1.4	.5	.2

ONE-WAY ANALYSIS OF VARIANCE PROGRAM : ANOVA

Analysis of Day: 1 / MALES

Group-no.: 1				
-1.300	- .900	- .600	- .900	
MEDIAN=	- .900	MEAN=	- .925	STD = .287
Group-no.: 2				
1.200	- .400	- .600	-2.100	
MEDIAN=	- .500	MEAN=	- .475	STD = 1.350
Group-no.: 3				
-1.700	-1.400	-1.300	-1.800	
MEDIAN=	-1.550	MEAN=	-1.550	STD = .238
Group-no.: 4				
-2.100	-1.000	-2.500	-2.800	
MEDIAN=	-2.300	MEAN=	-2.100	STD = .787
Group-no.: 5				
-5.500	-4.000	-2.700		
MEDIAN=	-4.000	MEAN=	-4.067	STD = 1.401

BOXs TEST FOR HOMOGENEITY OF VARIANCES AT P=.05000 LEVEL

CALCULATED F	D.F.s	PROBABILITY
2.6421	4 & 278.	.0335

HETEROGENEOUS VARIANCES (ONE-TAILED TEST)

ONE-WAY CLASSIFICATION ANALYSIS OF VARIANCE

SOURCE	SS	DF	MS	F	PROB
TREATMENT	25.94	4	6.4845	7.778	.002
ERROR	11.67	14	.83369		
TOTAL	37.61	18			

OVERALL SIGNIFICANCE AT 5.% (ONE-TAILED) LEVEL

GAMES AND HOWELL MODIFICATION OF
TUKEY-KRAMER'S HONESTLY SIGNIFICANT DIFFERENCE TEST
(WITH THE STUDENTIZED RANGE STATISTIC)

GROUPS COMPARED	CALCULATED TEST VALUE	DEGREES OF FREEDOM	PROBABILITY	CONCLUSION

5. % ONE-TAILED TEST				
1 AND 2	.92	3	.9550	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 2	.92	3	.9550	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 3	-4.74	6	.0782	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 3	4.74	6	.0782	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 4	-3.97	4	.1927	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 4	3.97	4	.1927	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 5	-5.41	2	.1809	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 5	5.41	2	.1809	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 3	-2.22	3	.5932	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 3	2.22	3	.5932	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 4	-2.94	5	.3510	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 4	2.94	5	.3510	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 5	-4.82	4	.1135	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 5	4.82	4	.1135	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
3 AND 4	-1.89	4	.6887	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
3 AND 4	1.89	4	.6887	NOT SIGNIFICANT
5. % ONE-TAILED TEST				

3 AND 5	-4.35	2	.2591	NOT SIGNIFICANT
5. % TWO-TAILED TEST				

3 AND 5	4.35	2	.2591	NOT SIGNIFICANT
5. % ONE-TAILED TEST				

4 AND 5	-3.09	3	.3718	NOT SIGNIFICANT
5. % TWO-TAILED TEST				

4 AND 5	3.09	3	.3718	NOT SIGNIFICANT

ONE-WAY ANALYSIS OF VARIANCE PROGRAM : ANOVA

Analysis of Day: 3 / MALES

```

Group-no.: 1
  1.200      2.200      2.000      2.500
MEDIAN=      2.100  MEAN=      1.975  STD =      .556

Group-no.: 2
  2.800      1.900      1.700      1.800
MEDIAN=      1.850  MEAN=      2.050  STD =      .507

Group-no.: 3
  3.000      2.300      2.100      3.100
MEDIAN=      2.650  MEAN=      2.625  STD =      .499

Group-no.: 4
  4.000      2.900      4.900      4.900
MEDIAN=      4.450  MEAN=      4.175  STD =      .950

Group-no.: 5
  3.100      3.800
MEDIAN=      3.450  MEAN=      3.450  STD =      .495

```

GROUP: 5 HAS LESS THAN 3 OBSERVATIONS, OMITTED FROM BOXs TEST
 BOXs TEST FOR HOMOGENEITY OF VARIANCES AT P=.05000 LEVEL

CALCULATED F	D.F.s	PROBABILITY
.5635	3 & 259.	.6439

HOMOGENEOUS VARIANCES (ONE-TAILED TEST)

ONE-WAY CLASSIFICATION ANALYSIS OF VARIANCE

SOURCE	SS	DF	MS	F	PROB
TREATMENT	13.50	4	3.3751	8.129	.002
ERROR	5.397	13	.41519		
TOTAL	18.90	17			

OVERALL SIGNIFICANCE AT 5.% (ONE-TAILED) LEVEL

GAMES AND HOWELL MODIFICATION OF
TUKEY-KRAMER'S HONESTLY SIGNIFICANT DIFFERENCE TEST
(WITH THE STUDENTIZED RANGE STATISTIC)

GROUPS COMPARED	CALCULATED TEST VALUE	DEGREES OF FREEDOM	PROBABILITY	CONCLUSION

5. % ONE-TAILED TEST				
1 AND 2	.28	6	1.0000	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 2	.28	6	1.0000	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 3	2.46	6	.4777	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 3	2.46	6	.4777	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 4	5.65	5	.0507	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 4	5.65	5	.0507	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 5	4.67	2	.2316	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 5	4.67	2	.2316	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 3	2.29	6	.5373	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 3	2.29	6	.5373	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 4	5.58	5	.0531	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 4	5.58	5	.0531	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 5	4.58	2	.2385	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 5	4.58	2	.2385	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
3 AND 4	4.09	5	.1519	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
3 AND 4	4.09	5	.1519	NOT SIGNIFICANT
5. % ONE-TAILED TEST				

3 AND 5	2.71	2	.4998	NOT SIGNIFICANT
5. % TWO-TAILED TEST				

3 AND 5	2.71	2	.4998	NOT SIGNIFICANT
5. % ONE-TAILED TEST				

4 AND 5	-1.74	4	.7409	NOT SIGNIFICANT
5. % TWO-TAILED TEST				

4 AND 5	1.74	4	.7409	NOT SIGNIFICANT

ONE-WAY ANALYSIS OF VARIANCE PROGRAM : ANOVA

Analysis of Day: 7 / MALES

```

Group-no.: 1
  2.500      1.300      .900      2.300
MEDIAN=     1.800  MEAN=     1.750  STD =     .772

Group-no.: 2
  2.900      1.900      2.800      2.600
MEDIAN=     2.700  MEAN=     2.550  STD =     .451

Group-no.: 3
  2.000      2.300      2.500      2.300
MEDIAN=     2.300  MEAN=     2.275  STD =     .206

Group-no.: 4
  5.300      5.600      4.700      4.300
MEDIAN=     5.000  MEAN=     4.975  STD =     .585

Group-no.: 5
  4.400      4.100
MEDIAN=     4.250  MEAN=     4.250  STD =     .212

```

GROUP: 5 HAS LESS THAN 3 OBSERVATIONS, OMITTED FROM BOXs TEST
 BOXs TEST FOR HOMOGENEITY OF VARIANCES AT P=.05000 LEVEL

CALCULATED F	D.F.s	PROBABILITY
1.2989	3 & 259.	.2743

HOMOGENEOUS VARIANCES (ONE-TAILED TEST)

ONE-WAY CLASSIFICATION ANALYSIS OF VARIANCE

SOURCE	SS	DF	MS	F	PROB
TREATMENT	27.86	4	6.9657	25.154	.000
ERROR	3.600	13	.27692		
TOTAL	31.46	17			

OVERALL SIGNIFICANCE AT 5.% (ONE-TAILED) LEVEL

GAMES AND HOWELL MODIFICATION OF
TUKEY-KRAMER'S HONESTLY SIGNIFICANT DIFFERENCE TEST
(WITH THE STUDENTIZED RANGE STATISTIC)

GROUPS COMPARED	CALCULATED TEST VALUE	DEGREES OF FREEDOM	PROBABILITY	CONCLUSION
5. % ONE-TAILED TEST				
1 AND 2	2.53	5	.4662	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 2	2.53	5	.4662	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 3	1.86	3	.7059	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 3	1.86	3	.7059	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 4	9.41	6	.0031	SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 4	9.41	6	.0031	SIGNIFICANT
5. % ONE-TAILED TEST				
1 AND 5	8.53	4	.0172	SIGNIFICANT
5. % TWO-TAILED TEST				
1 AND 5	8.53	4	.0172	SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 3	-1.57	4	.7967	NOT SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 3	1.57	4	.7967	NOT SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 4	9.28	6	.0034	SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 4	9.28	6	.0034	SIGNIFICANT
5. % ONE-TAILED TEST				
2 AND 5	8.88	4	.0148	SIGNIFICANT
5. % TWO-TAILED TEST				
2 AND 5	8.88	4	.0148	SIGNIFICANT
5. % ONE-TAILED TEST				
3 AND 4	12.31	4	.0019	SIGNIFICANT
5. % TWO-TAILED TEST				
3 AND 4	12.31	4	.0019	SIGNIFICANT
5. % ONE-TAILED TEST				

3 AND 5	15.35	2	.0010	SIGNIFICANT
5. % TWO-TAILED TEST				

3 AND 5	15.35	2	.0010	SIGNIFICANT
5. % ONE-TAILED TEST				

4 AND 5	-3.12	4	.3325	NOT SIGNIFICANT
5. % TWO-TAILED TEST				

4 AND 5	3.12	4	.3325	NOT SIGNIFICANT

Clinical observations - Rats

Test compound: Desmodur VP LS 2294

Study-no: T3067460 (Rats)

Concentration: 2 mg/m3 air / Sex: MALES

Observation	Day Relative							
	0	1	2	3	4	5	6	7
Motility reduced	0	0	0	0	0	0	0	0
Labored breathing pattern	0	0	0	0	0	0	0	0
Tachypnea	0	0	0	0	0	0	0	0
Hair-coat ungroomed	0	0	0	0	0	0	0	0
Surviving animals (N)	4	4	4	4	4	4	4	0

Legend: n = number of animals with signs

Test compound: Desmodur VP LS 2294

Study-no: T3067460 (Rats)

Concentration: 10 mg/m3 air / Sex: MALES

Observation	Day Relative							
	0	1	2	3	4	5	6	7
Motility reduced	0	0	0	0	0	0	0	0
Labored breathing pattern	0	0	0	0	0	0	0	0
Tachypnea	0	0	0	0	0	0	0	0
Hair-coat ungroomed	0	0	0	0	0	0	0	0
Surviving animals (N)	4	4	4	4	4	4	4	0

Legend: n = number of animals with signs

Clinical observations - Rats

Test compound: Desmodur VP LS 2294

Study-no: T3067460 (Rats)

Concentration: 50 mg/m3 air / Sex: MALES

Observation	Day Relative							
	0	1	2	3	4	5	6	7
Motility reduced	0	0	0	0	0	0	0	0
Labored breathing pattern	0	0	0	0	0	0	0	0
Tachypnea	0	0	0	0	0	0	0	0
Hair-coat ungroomed	0	0	0	0	0	0	0	0
Surviving animals (N)	4	4	4	4	4	4	4	0

Legend: n = number of animals with signs

Test compound: Desmodur VP LS 2294

Study-no: T3067460 (Rats)

Concentration: 100 mg/m3 air / Sex: MALES

Observation	Day Relative							
	0	1	2	3	4	5	6	7
Motility reduced	4	0	0	0	0	0	0	0
Labored breathing pattern	4	2	0	0	0	0	0	0
Tachypnea	0	2	0	0	0	0	0	0
Hair-coat ungroomed	0	1	0	0	0	0	0	0
Surviving animals (N)	4	4	4	4	4	4	4	0

Legend: n = number of animals with signs

Test compound: Desmodur VP LS 2294
 Study-no: T3067460 (Rats)

Sign: Motility reduced

		Target Concentration - mg/m3 air			
		2	10	50	100
Sex		M	M	M	M
Day		n/N	n/N	n/N	n/N
0		0/ 4	0/ 4	0/ 4	4/ 4
1		0/ 4	0/ 4	0/ 4	0/ 4
2		0/ 4	0/ 4	0/ 4	0/ 4
3		0/ 4	0/ 4	0/ 4	0/ 4
4		0/ 4	0/ 4	0/ 4	0/ 4
5		0/ 4	0/ 4	0/ 4	0/ 4
6		0/ 4	0/ 4	0/ 4	0/ 4
7		0/ 0	0/ 0	0/ 0	0/ 0

Legend: n = number of animals with signs, N = survivors
 M = males, F = females

Sign: Labored breathing pattern

		Target Concentration - mg/m3 air			
		2	10	50	100
Sex		M	M	M	M
Day		n/N	n/N	n/N	n/N
0		0/ 4	0/ 4	0/ 4	4/ 4
1		0/ 4	0/ 4	0/ 4	2/ 4
2		0/ 4	0/ 4	0/ 4	0/ 4
3		0/ 4	0/ 4	0/ 4	0/ 4
4		0/ 4	0/ 4	0/ 4	0/ 4
5		0/ 4	0/ 4	0/ 4	0/ 4
6		0/ 4	0/ 4	0/ 4	0/ 4
7		0/ 0	0/ 0	0/ 0	0/ 0

Legend: n = number of animals with signs, N = survivors
 M = males, F = females

Test compound: Desmodur VP LS 2294
Study-no: T3067460 (Rats)

Sign: Tachypnea

		Target Concentration - mg/m3 air			
		2	10	50	100
		M	M	M	M
Day	Sex	n/N	n/N	n/N	n/N
0		0/ 4	0/ 4	0/ 4	0/ 4
1		0/ 4	0/ 4	0/ 4	2/ 4
2		0/ 4	0/ 4	0/ 4	0/ 4
3		0/ 4	0/ 4	0/ 4	0/ 4
4		0/ 4	0/ 4	0/ 4	0/ 4
5		0/ 4	0/ 4	0/ 4	0/ 4
6		0/ 4	0/ 4	0/ 4	0/ 4
7		0/ 0	0/ 0	0/ 0	0/ 0

Legend: n = number of animals with signs, N = survivors
M = males, F = females

Sign: Hair-coat ungroomed

		Target Concentration - mg/m3 air			
		2	10	50	100
		M	M	M	M
Day	Sex	n/N	n/N	n/N	n/N
0		0/ 4	0/ 4	0/ 4	0/ 4
1		0/ 4	0/ 4	0/ 4	1/ 4
2		0/ 4	0/ 4	0/ 4	0/ 4
3		0/ 4	0/ 4	0/ 4	0/ 4
4		0/ 4	0/ 4	0/ 4	0/ 4
5		0/ 4	0/ 4	0/ 4	0/ 4
6		0/ 4	0/ 4	0/ 4	0/ 4
7		0/ 0	0/ 0	0/ 0	0/ 0

Legend: n = number of animals with signs, N = survivors
M = males, F = females

Test compound: Desmodur VP LS 2294
 Study-no: T3067460 (Rats)

Sign: Motility reduced

		Target Concentration - mg/m3 air											
		10				50				100			
		M				M				M			
Sex	Day	l	m	s	N	l	m	s	N	l	m	s	N
	0	0	0	0	4	0	0	0	4	4	0	0	4
	1	0	0	0	4	0	0	0	4	0	0	0	4
	2	0	0	0	4	0	0	0	4	0	0	0	4
	3	0	0	0	4	0	0	0	4	0	0	0	4
	4	0	0	0	4	0	0	0	4	0	0	0	4
	5	0	0	0	4	0	0	0	4	0	0	0	4
	6	0	0	0	4	0	0	0	4	0	0	0	4
	7	0	0	0	0	0	0	0	0	0	0	0	0

Legend: l = slight, m = moderate, s = severe, N = survivors, M = males, F = females

Test compound: Desmodur VP LS 2294
Study-no: T3067460 (Rats)

Sign: Labored breathing pattern

		Target Concentration - mg/m3 air											
		2				10				50			
		M				M				M			
		l	m	s	N	l	m	s	N	l	m	s	N
Day	Sex	l	m	s	N	l	m	s	N	l	m	s	N
0		0	0	0	4	0	0	0	4	0	0	0	4
1		0	0	0	4	0	0	0	4	2	0	0	4
2		0	0	0	4	0	0	0	4	0	0	0	4
3		0	0	0	4	0	0	0	4	0	0	0	4
4		0	0	0	4	0	0	0	4	0	0	0	4
5		0	0	0	4	0	0	0	4	0	0	0	4
6		0	0	0	4	0	0	0	4	0	0	0	4
7		0	0	0	0	0	0	0	0	0	0	0	0

Legend: l = slight, m = moderate, s = severe, N = survivors, M = males, F = females

Test compound: Desmodur VP LS 2294
 Study-no: T3067460 (Rats)

Sign: Tachypnea

		Target Concentration - mg/m3 air											
		2				10				50			
		M				M				M			
Sex	Day	1	m	s	N	1	m	s	N	1	m	s	N
	0	0	0	0	4	0	0	0	4	0	0	0	4
	1	0	0	0	4	0	0	0	4	2	0	0	4
	2	0	0	0	4	0	0	0	4	0	0	0	4
	3	0	0	0	4	0	0	0	4	0	0	0	4
	4	0	0	0	4	0	0	0	4	0	0	0	4
	5	0	0	0	4	0	0	0	4	0	0	0	4
	6	0	0	0	4	0	0	0	4	0	0	0	4
	7	0	0	0	0	0	0	0	0	0	0	0	0

Legend: 1 = slight, m = moderate, s = severe, N = survivors, M = males, F = females

Test compound: Desmodur VP LS 2294
 Study-no: T3067460 (Rats)

Sign: Hair-coat ungroomed

		Target Concentration - mg/m3 air											
		10				50				100			
		M		N		M		N		M		N	
Day	Sex	1	m	s	N	1	m	s	N	1	m	s	N
0		0	0	0	4	0	0	0	4	0	0	0	4
1		0	0	0	4	0	0	0	4	1	0	0	4
2		0	0	0	4	0	0	0	4	0	0	0	4
3		0	0	0	4	0	0	0	4	0	0	0	4
4		0	0	0	4	0	0	0	4	0	0	0	4
5		0	0	0	4	0	0	0	4	0	0	0	4
6		0	0	0	4	0	0	0	4	0	0	0	4
7		0	0	0	0	0	0	0	0	0	0	0	0

Legend: 1 = slight, m = moderate, s = severe, N = survivors, M = males, F = females

Clinical observations - Mice

Test compound: Desmodur VP LS 2294

Study-no: T3067460 (Mice)

Concentration: 2 mg/m3 air / Sex: MALES

Observation	Day Relative							
	0	1	2	3	4	5	6	7
Motility reduced	0	0	0	0	0	0	0	0
Labored breathing pattern	0	0	0	0	0	0	0	0
Unregular breathing pattern	0	0	0	0	0	0	0	0
Surviving animals (N)	4	4	4	4	4	4	4	0

Legend: n = number of animals with signs

Test compound: Desmodur VP LS 2294

Study-no: T3067460 (Mice)

Concentration: 10 mg/m3 air / Sex: MALES

Observation	Day Relative							
	0	1	2	3	4	5	6	7
Motility reduced	0	0	0	0	0	0	0	0
Labored breathing pattern	0	0	0	0	0	0	0	0
Unregular breathing pattern	3	0	0	0	0	0	0	0
Surviving animals (N)	4	4	4	4	4	4	4	0

Legend: n = number of animals with signs

Clinical observations - Mice

Test compound: Desmodur VP LS 2294

Study-no: T3067460 (Mice)

Concentration: 50 mg/m3 air / Sex: MALES

Observation	Day Relative							
	0	1	2	3	4	5	6	7
Motility reduced	0	0	0	0	0	0	0	0
Labored breathing pattern	0	0	0	0	0	0	0	0
Unregular breathing pattern	3	0	0	0	0	0	0	0
Surviving animals (N)	4	4	4	4	4	4	4	0

Legend: n = number of animals with signs

Test compound: Desmodur VP LS 2294

Study-no: T3067460 (Mice)

Concentration: 100 mg/m3 air / Sex: MALES

Observation	Day Relative							
	0	1	2	3	4	5	6	7
Motility reduced	4	0	0	0	0	0	0	0
Labored breathing pattern	4	0	0	0	0	0	0	0
Unregular breathing pattern	0	0	0	0	0	0	0	0
Surviving animals (N)	4	2	2	2	2	2	2	0

Legend: n = number of animals with signs

Test compound: Desmodur VP LS 2294
 Study-no: T3067460 (Mice)

Sign: Motility reduced

		Target Concentration - mg/m3 air			
		2	10	50	100
		M	M	M	M
Day	Sex	n/N	n/N	n/N	n/N
0		0/ 4	0/ 4	0/ 4	4/ 4
1		0/ 4	0/ 4	0/ 4	0/ 2
2		0/ 4	0/ 4	0/ 4	0/ 2
3		0/ 4	0/ 4	0/ 4	0/ 2
4		0/ 4	0/ 4	0/ 4	0/ 2
5		0/ 4	0/ 4	0/ 4	0/ 2
6		0/ 4	0/ 4	0/ 4	0/ 2
7		0/ 0	0/ 0	0/ 0	0/ 0

Legend: n = number of animals with signs, N = survivors
 M = males, F = females

Sign: Labored breathing pattern

		Target Concentration - mg/m3 air			
		2	10	50	100
		M	M	M	M
Day	Sex	n/N	n/N	n/N	n/N
0		0/ 4	0/ 4	0/ 4	4/ 4
1		0/ 4	0/ 4	0/ 4	0/ 2
2		0/ 4	0/ 4	0/ 4	0/ 2
3		0/ 4	0/ 4	0/ 4	0/ 2
4		0/ 4	0/ 4	0/ 4	0/ 2
5		0/ 4	0/ 4	0/ 4	0/ 2
6		0/ 4	0/ 4	0/ 4	0/ 2
7		0/ 0	0/ 0	0/ 0	0/ 0

Legend: n = number of animals with signs, N = survivors
 M = males, F = females

Test compound: Desmodur VP LS 2294
Study-no: T3067460 (Mice)

Sign: Unregular breathing pattern

		Target Concentration - mg/m3 air			
		2	10	50	100
Sex		M	M	M	M
Day		n/N	n/N	n/N	n/N
0		0/ 4	3/ 4	3/ 4	0/ 4
1		0/ 4	0/ 4	0/ 4	0/ 2
2		0/ 4	0/ 4	0/ 4	0/ 2
3		0/ 4	0/ 4	0/ 4	0/ 2
4		0/ 4	0/ 4	0/ 4	0/ 2
5		0/ 4	0/ 4	0/ 4	0/ 2
6		0/ 4	0/ 4	0/ 4	0/ 2
7		0/ 0	0/ 0	0/ 0	0/ 0

Legend: n = number of animals with signs, N = survivors
M = males, F = females

Test compound: Desmondur VP LS 2294
 Study-no: T3067460 (Mice)

Sign: Motility reduced

		Target Concentration - mg/m3 air											
		2				10				50			
		M				M				M			
		1 m s N				1 m s N				1 m s N			
Day	Sex	1	m	s	N	1	m	s	N	1	m	s	N
0		0	0	0	4	0	0	0	4	0	0	0	4
1		0	0	0	4	0	0	0	4	0	0	0	2
2		0	0	0	4	0	0	0	4	0	0	0	2
3		0	0	0	4	0	0	0	4	0	0	0	2
4		0	0	0	4	0	0	0	4	0	0	0	2
5		0	0	0	4	0	0	0	4	0	0	0	2
6		0	0	0	4	0	0	0	4	0	0	0	2
7		0	0	0	0	0	0	0	0	0	0	0	0

Legend: 1 = slight, m = moderate, s = severe, N = survivors, M = males, F = females

Test compound: Desmodur VP LS 2294
 Study-no: T3067460 (Mice)

Sign: Labored breathing pattern

		Target Concentration - mg/m3 air											
		2				10				50			
		M				M				M			
Sex	Day	l	m	s	N	l	m	s	N	l	m	s	N
	0	0	0	0	4	0	0	0	4	0	0	0	4
	1	0	0	0	4	0	0	0	4	0	0	0	2
	2	0	0	0	4	0	0	0	4	0	0	0	2
	3	0	0	0	4	0	0	0	4	0	0	0	2
	4	0	0	0	4	0	0	0	4	0	0	0	2
	5	0	0	0	4	0	0	0	4	0	0	0	2
	6	0	0	0	4	0	0	0	4	0	0	0	2
	7	0	0	0	0	0	0	0	0	0	0	0	0

Legend: l = slight, m = moderate, s = severe, N = survivors, M = males, F = females

Test compound: Desmodur VP LS 2294
 Study-no: T3067460 (Mice)

Sign: Unregular breathing pattern

Day	Sex	Target Concentration - mg/m3 air											
		2				10				50			
		M		F		M		F		M		F	
		l	s	l	s	l	s	l	s	l	s	l	s
0		0	0	0	0	3	0	0	0	4	0	0	0
1		0	0	0	0	0	0	0	0	4	0	0	0
2		0	0	0	0	0	0	0	0	4	0	0	0
3		0	0	0	0	0	0	0	0	4	0	0	0
4		0	0	0	0	0	0	0	0	4	0	0	0
5		0	0	0	0	0	0	0	0	4	0	0	0
6		0	0	0	0	0	0	0	0	4	0	0	0
7		0	0	0	0	0	0	0	0	0	0	0	0

Legend: l = slight, m = moderate, s = severe, N = survivors, M = males, F = females

Respiratory function measurements - Rats

RD50 Evaluation

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Print-Date: 20.10.1998

Statistics printout

Group designation: 1

Study-Nr.: T3067460
Test Substance: Desmodur VP LS 2294
Title: RD50 / Rat

Measuring results	Means[abs]	SD[abs]	Min[%]	Max[%]
Peak Inspiratory Flow [ml/min]:	12.0	1.3	80.5	115.0
Peak Expiratory Flow [ml/min]:	11.8	1.3	77.9	112.9
Tidal Volume [ml]:	1.4	0.1	90.3	118.0
Minute Volume [ml/min]:	238.7	25.4	79.1	111.2
Respiratory Rate [breaths/min]:	173.0	15.6	74.7	112.5
Expiratory Time [msec]:	192.8	19.5	86.5	137.1
Inspiratory Time [msec]:	155.8	10.2	91.0	131.7
Apnea Time [msec]:	6.3	1.1	86.4	261.6
Apnea Logging Period [#]:	2.0	0.5	62.1	439.8
ET/IT:	1.2	0.1	95.2	114.0
PIF/PEF:	1.0	0.0	90.0	114.5
PEF*(IT+ET)/TV * 1/1000:	2.9	0.1	88.9	112.6
TV/IT:	0.0	0.0	84.8	110.6

abs: absolute data for adaptation period

%: rel. change to adaptation period

RD50 Evaluation

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Print-Date: 20.10.1998

Statistics printout

Group designation: 2

Study-Nr.: T3067460
Test Substance: Desmodur VP LS 2294
Title: RD50 / Rat

Measuring results	Means[abs]	SD[abs]	Min[%]	Max[%]
Peak Inspiratory Flow [ml/min]:	12.5	0.7	77.5	113.0
Peak Expiratory Flow [ml/min]:	11.5	0.8	74.0	117.0
Tidal Volume [ml]:	1.5	0.0	94.7	110.1
Minute Volume [ml/min]:	240.4	8.5	78.1	105.8
Respiratory Rate [breaths/min]:	166.5	8.7	76.4	106.1
Expiratory Time [msec]:	203.5	9.4	93.1	131.2
Inspiratory Time [msec]:	156.2	7.8	94.2	130.6
Apnea Time [msec]:	5.8	0.6	85.7	143.9
Apnea Logging Period [#]:	1.9	0.5	43.2	175.7
ET/IT:	1.3	0.0	94.1	109.4
PIF/PEF:	1.1	0.0	82.1	110.5
PEF*(IT+ET)/TV * 1/1000:	2.9	0.1	91.0	125.6
TV/IT:	0.0	0.0	78.5	105.2

abs: absolute data for adaptation period

%: rel. change to adaptation period

RD50 Evaluation

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Print-Date: 20.10.1998

Statistics printout

Group designation: 3

Study-Nr.: T3067460
Test Substance: Desmodur VP LS 2294
Title: RD50 / Rat

Measuring results	Means[abs]	SD[abs]	Min[%]	Max[%]
Peak Inspiratory Flow [ml/min]:	11.2	1.0	81.9	116.7
Peak Expiratory Flow [ml/min]:	11.7	0.8	69.0	109.3
Tidal Volume [ml]:	1.3	0.0	82.2	108.5
Minute Volume [ml/min]:	221.9	16.5	80.2	113.6
Respiratory Rate [breaths/min]:	172.1	11.4	85.9	113.8
Expiratory Time [msec]:	198.1	14.9	87.9	116.6
Inspiratory Time [msec]:	156.1	9.2	89.2	112.3
Apnea Time [msec]:	6.3	0.9	88.8	152.8
Apnea Logging Period [#]:	2.0	0.7	73.4	296.2
ET/IT:	1.3	0.1	91.8	107.9
PIF/PEF:	1.0	0.0	94.8	125.7
PEF*(IT+ET)/TV * 1/1000:	3.1	0.1	82.7	105.7
TV/IT:	0.0	0.0	77.2	112.3

abs: absolute data for adaptation period

%: rel. change to adaptation period

RD50 Evaluation

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Print-Date: 20.10.1998

Statistics printout

Group designation: 4

Study-Nr.: T3067460
Test Substance: Desmodur VP LS 2294
Title: RD50 / Rat

Measuring results	Means[abs]	SD[abs]	Min[%]	Max[%]
Peak Inspiratory Flow [ml/min]:	9.5	0.5	80.6	128.4
Peak Expiratory Flow [ml/min]:	9.1	0.5	83.8	132.4
Tidal Volume [ml]:	1.2	0.0	62.5	106.2
Minute Volume [ml/min]:	187.8	7.4	76.5	123.9
Respiratory Rate [breaths/min]:	159.6	8.0	83.6	138.7
Expiratory Time [msec]:	210.6	9.4	61.8	117.9
Inspiratory Time [msec]:	165.0	7.1	65.7	125.9
Apnea Time [msec]:	6.5	0.7	92.1	873.7
Apnea Logging Period [#]:	2.3	0.6	77.8	2244.3
ET/IT:	1.3	0.0	75.7	128.5
PIF/PEF:	1.0	0.0	88.0	105.2
PEF*(IT+ET)/TV * 1/1000:	2.9	0.1	91.9	129.5
TV/IT:	0.0	0.0	78.9	113.8

abs: absolute data for adaptation period

%: rel. change to adaptation period

RD50 Evaluation

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Print-Date: 20.10.1998

Statistics printout

Group designation: 5

Study-Nr.: T3067460
Test Substance: Desmodur VP LS 2294
Title: RD50 / Rat

Measuring results	Means[abs]	SD[abs]	Min[%]	Max[%]
Peak Inspiratory Flow [ml/min]:	13.4	1.0	68.7	110.9
Peak Expiratory Flow [ml/min]:	11.0	1.2	80.9	123.6
Tidal Volume [ml]:	1.5	0.0	42.4	102.3
Minute Volume [ml/min]:	247.1	17.9	57.3	107.8
Respiratory Rate [breaths/min]:	163.8	10.7	92.7	157.5
Expiratory Time [msec]:	215.4	13.9	41.9	105.4
Inspiratory Time [msec]:	152.4	8.2	64.0	116.3
Apnea Time [msec]:	5.4	0.9	91.0	1667.1
Apnea Logging Period [#]:	1.4	0.6	75.7	5654.1
ET/IT:	1.4	0.1	64.3	103.5
PIF/PEF:	1.2	0.1	71.8	104.7
PEF*(IT+ET)/TV * 1/1000:	2.6	0.1	96.4	136.3
TV/IT:	0.0	0.0	64.1	108.0

abs: absolute data for adaptation period

%: rel. change to adaptation period